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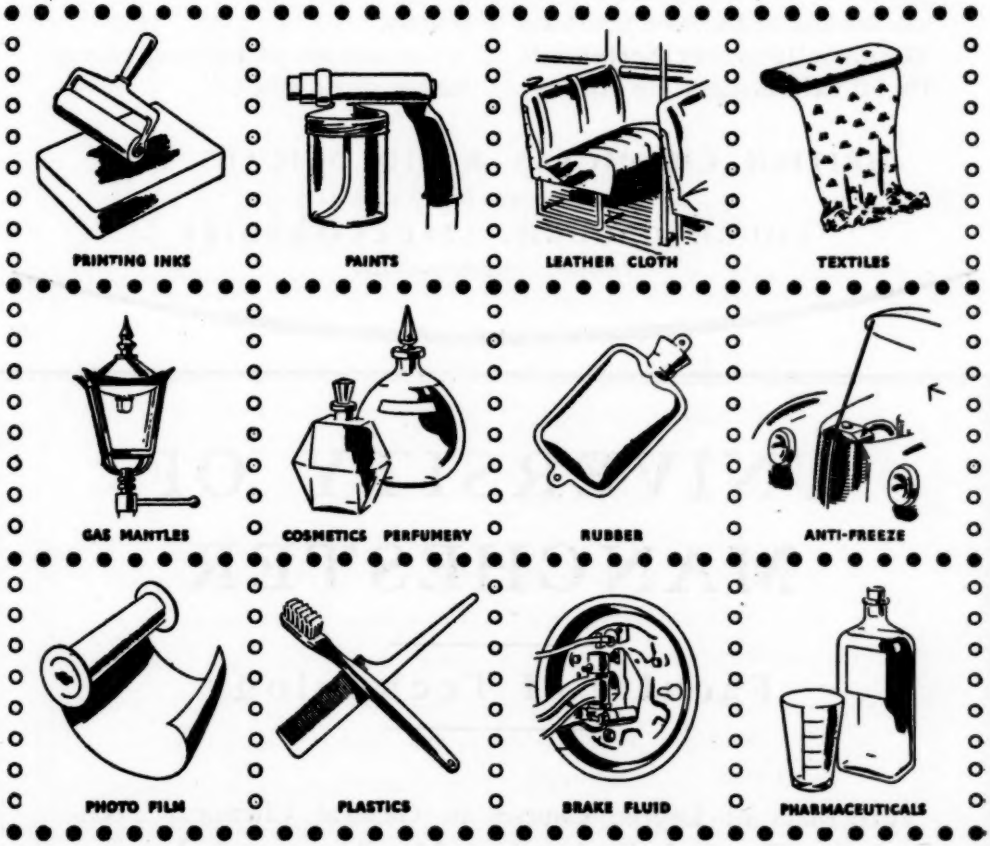

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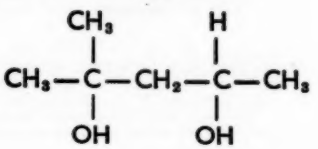

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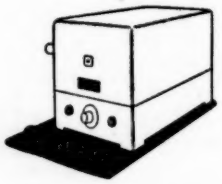

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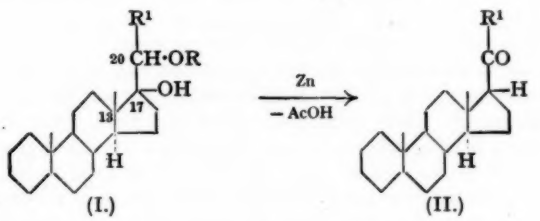
360. *Steroids and the Walden Inversion. Part V. The Serini Reaction.*

By C. W. Shoppee.

The mechanism of the Serini reaction is discussed. The reaction is considered to proceed by way of a 17 : 20-oxide; on this basis the stereochemical outcome at C_{17} of the reaction depends on the orientation of the oxide and the geometrical form of the transition state, and must always involve inversion of configuration at C_{17}. The existing evidence is shown to support this deduction, which is experimentally further substantiated by the conversion of Reichstein's substance O diacetate (a C_{17}-*normal* compound) into 17*iso*-*allo*pregnan-3β-ol-20-one.

In this series of papers it is intended to examine the stereochemical course of substitution reactions at the various positions in the steroid nucleus. Previous communications have dealt with certain aspects of substitution at C_3; the present paper deals with a reaction involving substitution at C_{17}.

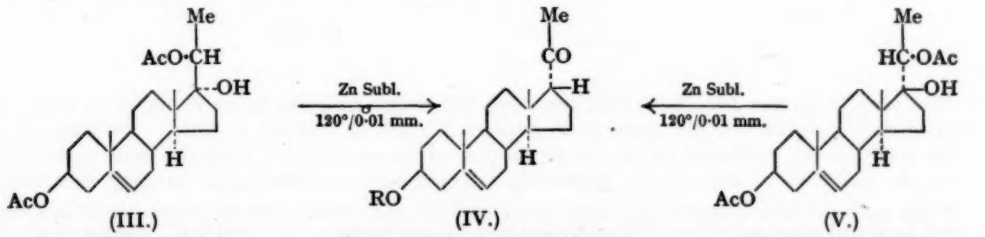
The Serini reaction was discovered by Slotta and Neisser (*Ber.*, 1938, **71**, 2342), and involves the conversion of the secondary acetate of a secondary–tertiary 1 : 2-glycol into a ketone by treatment with zinc dust. It was first employed in the steroid field by Serini, Logemann, and Hildebrand (*Ber.*, 1939, **72**, 391), and subsequently by the author (Shoppee and Reichstein, *Helv. Chim. Acta*, 1940, **23**, 729; Shoppee, *ibid.*, 1940, **23**, 925), and provides a valuable method



(I.) (II.)

for the transformation of a steroid 17 : 20-diol 20-acetate (I; R = Ac) into a steroid 20-ketone (II) with elimination of the elements of acetic acid. Fieser and Fieser (*Experientia*, 1948, **4**, 285) have recently given a concise and useful summary of the available examples.

There appears to be no direct evidence as to the mechanism of the Serini reaction, and Fieser and Fieser (*loc. cit.*) postulate that an enol-acetate, a 17 : 20-oxide, or a cyclic ortho-ester is formed as an intermediate by suitable elimination or cyclisation. On the basis of the stereochemical form (C_{13}-Me/C_{20}-R^1: *cis* or *trans*) of such an intermediate they achieve an empirical correlation of the existing data, and are able to account for the apparent production, through a *trans*-intermediate of the 17*iso*-20-ketone (IV; R = Ac) from *both* the 17*n*-20β-



(III.) (IV.) (V.)

M. p. 153° [a], 159° [b]; $[\alpha]_D$ − 36° [E][a], − 35° [A][b] [a]

M. p. 171°, $[\alpha]_D$ − 126° [E].[a] R = Ac.

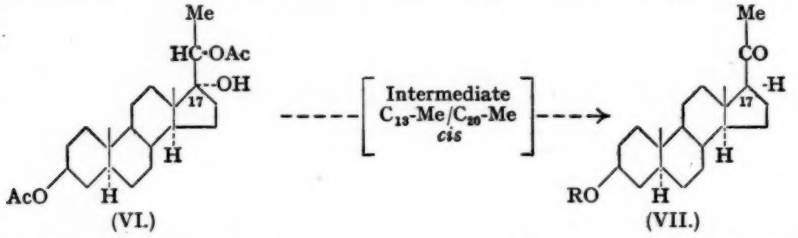
M. p. 182° [a], 185° [b]; $[\alpha]_D$ − 74° [E][a], − 73° [A].[b]

[a] Butenandt, Schmidt-Thomé, and Paul, *Ber.*, 1939, **72**, 1112.
[b] Prins and Reichstein, *Helv. Chim. Acta*, 1940, **23**, 1498.

[a] Here and later, [A], [C], [D], [E], and [M] indicate rotations determined in acetone, chloroform, dioxan, ethanol, and methanol, respectively.

acetate * (III) and the 17*iso*-20α-acetate * (V) (Butenandt, Schmidt-Thomé, and Paul, *Ber.*, 1939, **72**, 1112).

On the same stereochemical basis, however, Fieser and Fieser predict that a 17*n*-20α-acetate, *e.g.*, Reichstein's substance O diacetate (*allo*pregnane-3β : 17α : 20α-triol 3 : 20-diacetate) (VI) should undergo the Serini reaction to give, through a *cis*-intermediate, *allo*pregnan-3β-ol-20-one acetate (VII; R = Ac) with preservation of configuration at C_{17}:



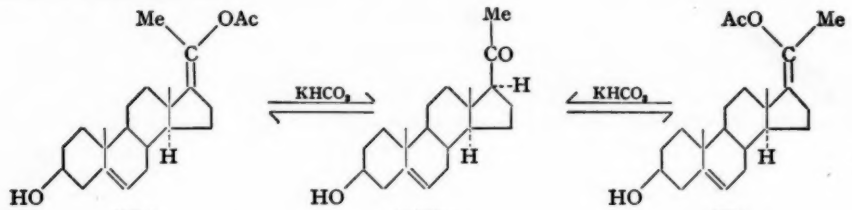
(VI.) (VII.)

Diol: m. p. 222°, $[\alpha]_D$ −13° [M].[c]
Diacetate: m. p. 250°, $[\alpha]_D$ −30° [A].[c]

Alcohol: m. p. 194°, $[\alpha]_D$ + 91° [E][d], + 96° [C].[c]
Acetate: m. p. 144°[d], $[\alpha]_D$ + 77° [C].[c]

[c] Steiger and Reichstein, *Helv. Chim. Acta*, 1938, **21**, 546.
[d] Butenandt and Mamoli, *Ber.*, 1935, **68**, 1847.
[e] Barton, private communication.

The application by Serini *et al.* (*loc. cit.*) of the procedure of Slotta and Neisser to an acetate (I; R = Ac) was preceded by the discovery by Serini and Logemann (*Ber.*, 1938, **71**, 1362) that treatment of the free 17 : 20-diol (I; R = H) with dehydrating agents (*e.g.*, formic acid) furnished the ketone (II) in small yield, presumably by pinacolic change. The pyrolytic procedure of Serini *et al.* (*loc. cit.*) (150°/0·0001 mm.) applied to an acetate (I; R = Ac) would not, however, be inconsistent with the occurrence of dehydration, whereby (I; R = Ac) could furnish the geometrically isomeric 17 : 20-unsaturated enol acetates (as IX; C_{13}-Me/C_{20}-Me *cis*), (as X; C_{13}-Me/C_{20}-Me *trans*). The conditions used by Serini can, however, with advantage be replaced by working in boiling toluene (~111°/760 mm.); further, the intermediate formation of an enol-acetate would require some operation involving hydrolysis in order to furnish the ketone (II), whereas the Serini reaction gives the ketonic product directly. Finally, Fieser and Huang-Minlon (private communication) have prepared from pregnenolone (VIII) the isomeric enol acetates (IX) and (X) (cf. also Marshall *et al.*, *J. Amer. Chem. Soc.*, 1948, **70**, 1837), and find that they are both very easily hydrolysed by cold aqueous-alcoholic potassium hydrogen carbonate and that they both yield pregnenolone. Enol acetates therefore cannot be intermediates in the Serini reaction.



(IX.) (VIII.) (X.)

The present author has since 1939 regarded the Serini reaction as an example of pinacolic electron displacement (cf. Shoppee, *Proc. Leeds Lit. Phil. Soc.*, 1928, **1**, 301). The first stage of the reaction is considered to be the separation of an acetate ion from the 20-acetate (XI) under the influence of zinc atoms (positively charged ions surrounded by valency electrons);

* The nomenclature proposed by Fieser and Fieser (*loc. cit.*) with a view to international adoption is used here and supersedes that formerly employed by the writer: " α " and " β " remain as trivial indices; (α) and (β), denoting orientation of nuclear substituents, become α and β, and their use is extended to C_{20} *only* in the side-chain for configurations which can be related to configuration at C_{17} in accordance with the convention suggested by Fieser and Fieser; α and β, denoting configuration in the side-chain, become a and b, *e.g.*, for configurations at C_{20} in the pregnane-3 : 20-diols and at C_{24} in the phytosterols which are not related to the configuration at C_{17}.

This system eliminates the use of parentheses but maintains the distinction which they signified; it can therefore be used in respect of continental nomenclature, *e.g.*, androstandiol-(3α, 11β)-on-17 in which the parentheses were and are still used only typographically.

FIG. 1.

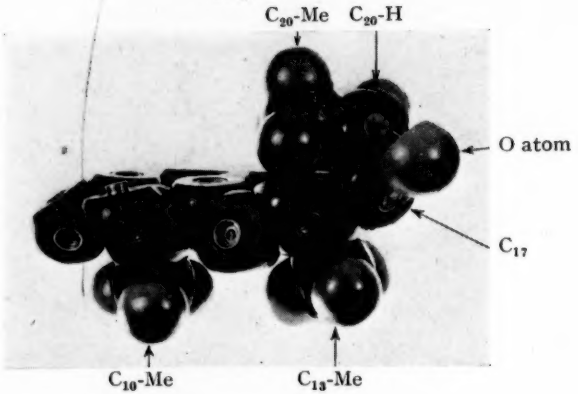


FIG. 2.

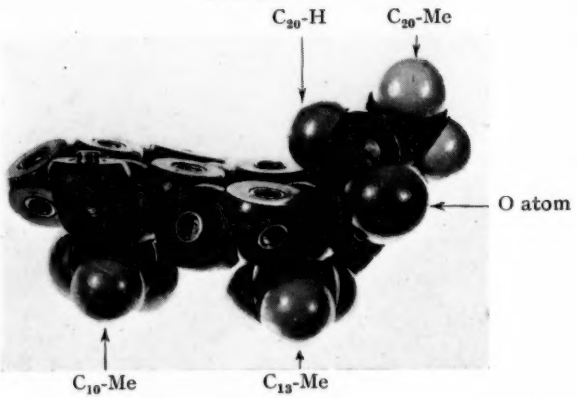


FIG. 3.

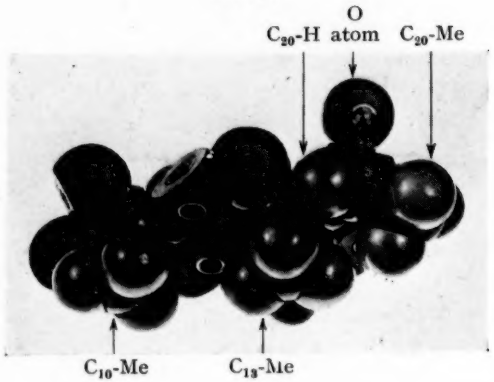
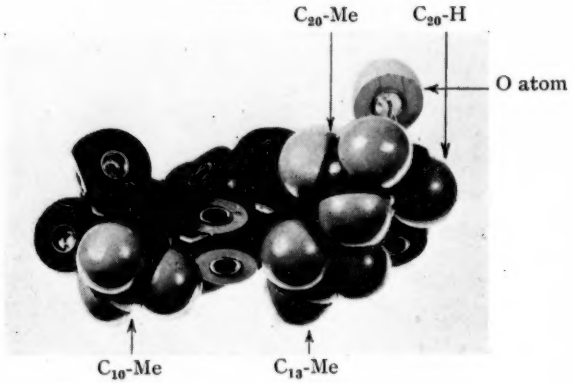
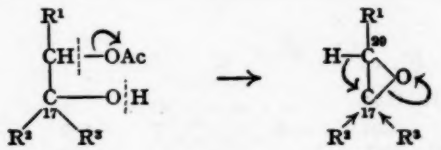


FIG. 4.



[*To face p.* 1673.

the function of the toluene appears to lie in bringing up the solute molecules in turn to the zinc surface. The resulting oxide (XII) then undergoes pinacolic rearrangement, many examples of which are known, and the direction of which depends on the relative electron-release capacities of the groups, R^1, R^2, and R^3 (Ingold, *Ann. Reports*, 1928, **25**, 135). In the case of steroid 17 : 20-oxides, usually $R^1 = -CH_3$ or $-CH_2{\cdot}OAc$, whilst $R^2 = C_{13}{<}^{C_{12}}_{C_{14}}{>}C_{13}$- and $R^3 = C_{13}{<}^{C_8}{>}C_{14}{\cdot}C_{15}{\cdot}C_{16}$-, *i.e.*, R^2 and R^3 are higher alkyl groups with electron-release capacities greater than that of the methyl group, so that the direction of rearrangement clearly must be that depicted in (XII), whereby the electron pair constituting the C_{17}–O bond leaves



(XI.) (XII.)

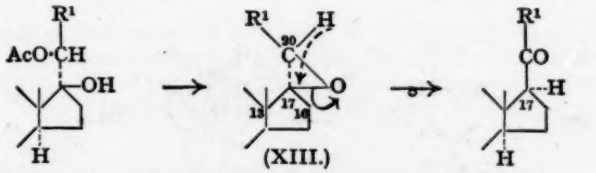
the octet of C_{17} to which the hydrogen atom attached to C_{20} migrates with its electron pair.*

The factors which determine the stereochemical outcome of the pinacolic rearrangement of the oxide (XII) are the geometry of the transition state and the orientation of the oxide ring.

In general, a transition state of linear type $X \ldots \overset{|}{C} \ldots Y$ is intrinsically more probable than one of pyramidal type $\overset{|}{C}{<}^{X}_{Y}$, because the repulsive interaction energy integrals will be minimised in the former type; in the present instance (XII), the formation of a linear-type transition state is to be expected and exemplifies the principle of *trans*-interchange in molecular rearrangements, and has as its inevitable consequence inversion of configuration at C_{17} in the ketonic product of the rearrangement.

In the formation from the acetate (XI) of the oxide (XII), the C_{17}–O bond remains unbroken and will therefore retain its original orientation; two types of oxide arise according as the oxide is a 17β : 20β- or a 17α : 20α-oxide. Although as will be shown, contrary to the suggestion of Fieser and Fieser, the orientation of the hydrogen atom (or, conversely, the orientation of the group R^1) attached to C_{20} relative to the C_{13}-methyl group is not a factor in the situation, four cases must be considered according as the initial acetate (XI) is a 20β- or a 20α-acetate.

Case 1.



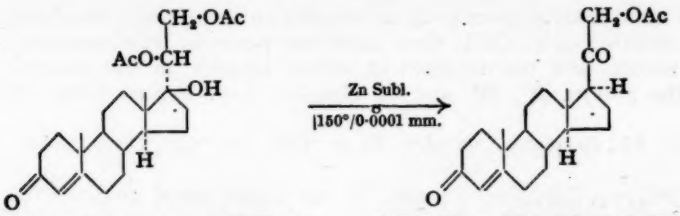
(XIII.)

17*iso*-20β-Acetate. 17β : 20β-Oxide (C_{13}-Me/C_{20}-R^1 : *cis*). 17*n*-20-Ketone.

[The dotted arrow from C_{20} to C_{17} indicates attack at the rear-face of C_{17}.]

The intermediate oxide (XIII) is a 17β : 20β-oxide derived from a 17*iso*-20β-acetate, and the case is represented by the original example of Serini *et al.* (*loc. cit.*), whereby 17*iso*-pregn-4-ene-17β : 20β : 21-triol-3-one diacetate (XIV) gives a 59% yield of 11-deoxycorticosterone acetate (XV). In the oxide (XIII), the hydrogen atom attached to C_{20}, which must migrate, lies well behind C_{16} (see Fig. 1) and, to furnish a linear transition state, $H \ldots \overset{|}{C} \ldots O$, must attack the rear-face of C_{17} with eventual inversion of configuration at C_{17} to give a 17*n*-ketone (as XV).

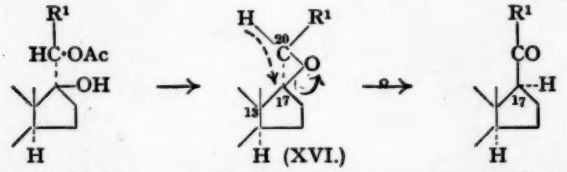
* The other possibilities, which do not appear to arise in the present instance, involve (i) migration of the C_{13}-methyl group to C_{17} (for an example see Shoppee and Prins, *Helv. Chim. Acta*, 1943, **26**, 1004) or (ii) migration of the C_{13}–C_{14} bond to give a C_{14}–C_{17} link.



(XIV.) M. p. 178°, $[\alpha]_D$ + 43° [D].[f] (XV.) M. p. 157°, $[\alpha]_D$ + 173° [D].[g]

[f] Serini, Logemann, and Hildebrand, *Ber.*, 1938, **71**, 1366.
[g] von Euw and Reichstein, *Helv. Chim. Acta*, 1942, **25**, 988.

Case 2.

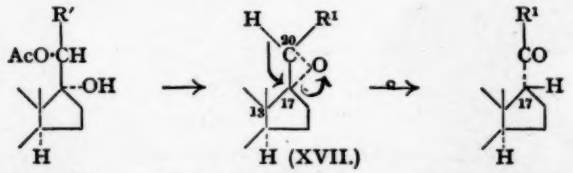


17*iso*-20α-Acetate. 17β : 20β-Oxide (C_{13}-Me/C_{20}-R^1 : *trans*). 17*n*-20-Ketone.

[The dotted arrow from C_{20}–H to C_{17} indicates attack at the rear-face of C_{17}.]

In case 2 the intermediate oxide (XVI) is again a 17β : 20β-oxide, but derived from a 17*iso*-20α-acetate, and the case should be represented by the rearrangement of 17*iso*-pregn-5-ene-3β : 17β : 20α-triol diacetate (V). In the oxide (XVI), the hydrogen atom attached to C_{20} lies directly behind C_{13} (see Fig. 2) and should attack the rear-face of C_{17} to furnish a linear transition state with eventual inversion of configuration at C_{17} to yield a 17*n*-ketone. Butenandt *et al.* (*loc. cit.*) describe in detail the rearrangement of one *or* the other of the isomerides (III) or (V) by sublimation with zinc dust (120°/0·01 mm.) to 17*iso*-pregn-5-en-3β-ol-20-one acetate (IV; R = Ac) in 64% yield, but it is impossible to tell from the text which isomeride was actually used. If these workers used the 17*n*-20β-isomeride (III), this result is in accord with theoretical expectation (see case 3); they state, however, without experimental details that *either* isomeride, (III) or (V), or a mixture, may be used and affords the same product (IV; R = Ac). As Fieser and Fieser (*loc. cit.*) write " this one reported instance of retention of configuration (V ⟶ IV), is not well documented and has not been confirmed; " the work is being repeated by Dr. Huang-Minlon in Prof. Fieser's laboratory.*

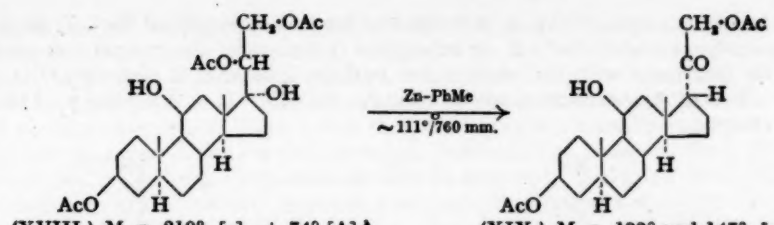
Case 3.



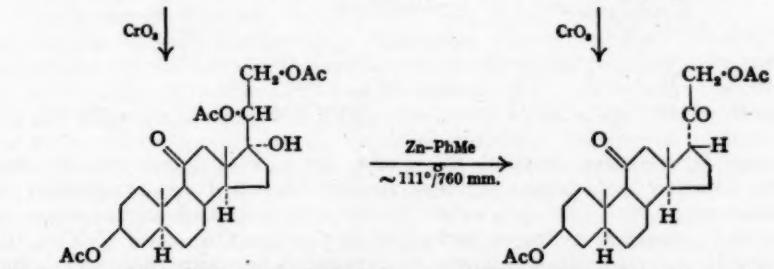
17*n*-20β-Acetate. 17α : 20α-Oxide (C_{13}-Me/C_{20}-R^1 : *trans*). 17*iso*-20-Ketone.

The intermediate oxide (XVII) is now a 17α : 20α-oxide derived from a 17*n*-20β-acetate, and the case is illustrated by three well-established examples: these are the conversion of Reichstein's substance A triacetate (XVIII) into substance 17*iso*-R diacetate (XIX) (Shoppee and Reichstein, *Helv. Chim. Acta*, 1940, **23**, 729), the conversion of the 11-keto-analogue (XX) of substance A triacetate into substance 17*iso*-N diacetate (XXI) (Shoppee and Reichstein, *loc. cit.*), and the preparation from pregn-4-ene-17α : 20β : 21-triol-3-one diacetate (XXII) of 17*iso*-11-deoxycorticosterone acetate (XXIII) (Shoppee, *Helv. Chim. Acta*, 1940, **23**, 925):

* Added, May 23rd, 1949.—Dr. Huang-Minlon has found that, contrary to the statement of Butenandt, Schmidt-Thomé, and Paul (*Ber.*, 1939, **72**, 1112), the acetate (V) undergoes the Serini reaction with inversion of configuration at C_{17} to give, not (IV; R = Ac), but the acetate of (VIII) (Fieser and Fieser, *Experientia*, 1948, **4**, 295, Addendum).

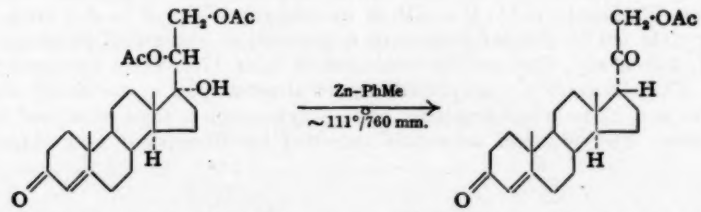


(XVIII.) M. p. 219°, $[\alpha]_D$ + 74° [A].[a] (XIX.) M. p. 133° and 147°, $[\alpha]_D$ − 60° [A].[a]



(XX.) M. p. 183°, 211°, $[\alpha]_D$ + 69° [A].[a] (XXI.) M. p. 131°, $[\alpha]_D$ − 44° [A].[a]

[a] Shoppee and Reichstein, *Helv. Chem. Acta*, 1940, **23**, 729.



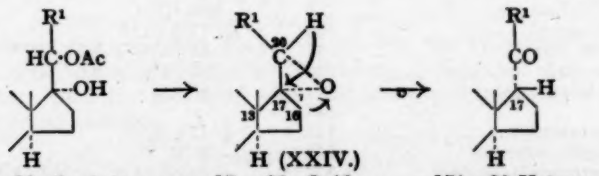
(XXII.) M. p. 170° and 190°.[f] (XXIII.) M. p. 137°, 174°; $[\alpha]_D$ − 26° [A].[f]

[f] Shoppee, *Helv. Chim. Acta*, 1940, **23**, 925.

If Butenandt, Schmidt-Thomé, and Paul (*loc. cit.*) actually used pregn-5-ene-3β : 17α : 20β-triol diacetate (III) in the preparation of 17*iso*-pregn-5-en-3β-ol-20-one acetate (IV; R = Ac), this would constitute a fourth example.

In (XVII), the hydrogen atom attached to C_{20} lies to the front of the general plane of the ring-system and above the C_{13}-angular methyl group (cf. Fig. 3); it should therefore attack the front face of C_{17} to furnish a linear transition state and, with consequent inversion at C_{17}, to give a 17*iso*-20-ketone. This is the result found experimentally in all three (? four) examples cited above.

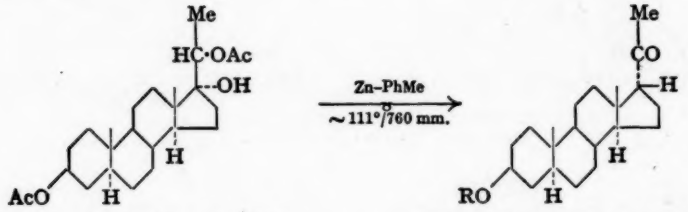
Case 4.



17*n*-20α-Acetate. 17α : 20α-Oxide (C_{13}-Me/C_{20}-R^1 : *cis*). H (XXIV.) 17*iso*-20-Ketone.

The intermediate oxide (XXIV) is again a 17α : 20α-oxide, but derived from a 17*n*-20α-acetate; the hydrogen atom attached to C_{20}, which must migrate, lies over and somewhat in front of C_{16} (cf. Fig. 4) and should attack the front face of C_{17} to give a linear transition state, with subsequent inversion at C_{17} to yield a 17*iso*-ketone, and not a 17*n*-ketone as predicted by Fieser and Fieser (*loc. cit.*).

There is no known example of case 4, but with the kind co-operation of Prof. T. Reichstein, who most generously provided 100 mg. of substance O diacetate, the matter has now been investigated. By treatment with zinc dust in hot toluene, substance O diacetate (VI) gives a 45% yield of 17iso-allo*pregnane*-3β-*ol*-20-*one acetate* (XXV; R = Ac), m. p. 118—119°, $[\alpha]_D$ −73° (in ethanol).



(VI.) M. p. 250°, $[\alpha]_D$ − 30° [A]. (XXV.) M. p. 118°, $[\alpha]_D$ − 73° [E].

This substance is identified beyond all doubt as a 17*iso*-compound by its large negative specific rotation (see later); it was further identified by comparison with a synthetic specimen, m. p. 119—122°, $[\alpha]_D$ −75° (EtOH), prepared as described below, and by hydrolysis with cold potassium hydrogen carbonate to the free 17*iso*-ketol (XXV; R = H), m. p. 139°, $[\alpha]_D$ −71° (in ethanol), which was also identified by comparison with a synthetic specimen, m. p. 139°, $[\alpha]_D$ −78° (in ethanol).

The 17*iso*-ketol (XXV; R = H), its acetate, and the derived 17*iso*-3 : 20-diketone were first described by Butenandt and Mamoli (*Ber.*, 1935, **68**, 1847); these workers found that treatment of the 17*n*-ketol (VII; R = H) or its acetate (VII; R = Ac) with hot alcoholic potassium hydroxide led to the production of a proportion (estimated at about 30%) of the 17*iso*-ketol, and, conversely, that similar treatment of their 17*iso*-ketol appeared to regenerate the 17*n*-ketol. They correctly interpreted these observations in terms of an equilibrium between the 17*n*- and 17*iso*-ketols resulting from a keto–enol change catalysed by hydroxide and ethoxide ions. The physical constants recorded by Butenandt and Mamoli are given in Table I.

TABLE I.

	17*iso*-Ketol.	17*iso*-Acetoxy-ketone.	17*iso*-3 : 20-Diketone.
M. p.	148°	101°	134—135°
$[\alpha]_D$ (EtOH)	+6°	—	−14·5°

TABLE II.

	M. p.	$[\alpha]_D$.	$[M]_D$.	$\Delta[M]_D$.
17*n*-Pregn-5-en-3β-ol-20-one	190°	+ 28° [E][1], + 25° [C] [2]	+ 88°	− 532°
17*iso*- ,, ,,	172	− 140·5 [E] [1]	− 444	
17*n*- ,, ,, acetate	146	+ 20 [E][1], + 14 [C] [2]	+ 72	− 523
17*iso*- ,, ,, ,,	170	− 126 [E] [1]	− 451	
Substance P diacetate	208	+ 44·5 [D] [4]	+ 193	− 488
,, 17*iso*-P diacetate	159	− 68 [D] [4]	− 295	
Substance N diacetate	144	+ 77·5 [A] [3]	+ 335	− 525
,, 17*iso*-N diacetate	131	− 44 [A][3], + 85·6 [D] [4]	− 190	
Substance R diacetate	173	+ 92 [A][4], + 83·7 [D] [4]	+ 364 *	− 624
,, 17*iso*-R diacetate	133 and 147	− 60 [A] [3]	− 260	
11-Deoxycorticosterone	141	+ 178 [E] [5]	+ 587	− 785
17*iso*-11-Deoxycorticosterone	179	− 6 [E] [6]	− 198	
11-Deoxycorticosterone acetate	157	+ 169·5 [A][6], + 164 [A][4], + 174 [D] [4]	+ 665	− 816
17*iso*-11-11-Deoxy ,,	137 and 174	− 26 [A] [6]	− 151	

* Owing to the unusual circumstance that the rotation in acetone is greater than that in dioxan, the value in dioxan has been preferred.

[1] Butenandt and Fleischer, *Ber.*, 1937, **70**, 96. [2] D. H. R. Barton, private communication. [3] Shoppee and Reichstein, *Helv. Chim. Acta*, 1940, **23**, 729. [4] von Euw and Reichstein, *ibid.*, 1942, **25**, 988. [5] Steiger and Reichstein, *ibid.*, 1937, **20**, 1164. [6] Shoppee, *ibid.*, 1940, **23**, 925.

A specimen (15 mg.) of the reputed 17*iso*-ketol, m. p. 147° (in a capillary tube), prepared by the method of Butenandt and Mamoli by Dr. D. H. R. Barton and kindly made available by him, had $[\alpha]_D^{28°}$ $-1° \pm 3°$ in ethanol, but, when examined microscopically on a Kofler block, behaved as a mixture rather than as a pure individual, commencing to melt at 135° to give a turbid liquid at about 150°, from which the last crystalline material disappeared only at 157°; and in fact the experimental details given by Butenandt and Mamoli show that their " pure " 17*iso*-ketol, m. p. 148°, was contaminated with at least 15% of the 17*n*-ketol; thus by oxidation at 20° with chromium trioxide in acetic acid, isolation of the product by dilution with water, and crystallisation from ethanol—conditions under which tautomeric change would be unlikely and has been shown (see later) not to occur—90 mg. of the 17*iso*-ketol yielded 13 mg. of pure 17*n*-5-*allo*pregnane-3 : 20-dione, m. p. 200·5°, $[\alpha]_D$ +127° (in ethanol).

Calculations of molecular-rotation differences also show that the 17*iso*-compounds of Butenandt and Mamoli were contaminated with considerable quantities of their 17*n*-isomerides. 17*iso*-Pregnenolone (IV; R = H) and its acetate (IV; R = Ac), originally obtained by Butenandt, Schmidt-Thomé, and Paul (*Ber.*, 1939, **72**, 1112) by the Serini reaction, are characterised by relatively large negative rotatory powers as compared with their 17*n*-isomerides; Table II sets out the specific and molecular rotations for these substances and other 17-epimeric pairs, and the molecular-rotation differences.

Omitting the last two pairs, in which the effect of inversion of configuration at C_{17} is clear but the influence of the Δ^4-3-ketonic grouping is also apparent (cf. Barton and Cox, *J.*, 1948, 783), and taking for the change 17*n* ⟶ 17*iso* an average value $\Delta[M]_D = -538°$, we can use this difference to calculate approximate values for the molecular and specific rotations of the saturated 17*iso*-ketol and its acetate (XXV), and the related 17*iso*-3 : 20-diketone, from the experimentally determined specific rotations of their 17*n*-epimerides. The results of these calculations are given in Table III, and it is apparent from a comparison with Table I that Butenandt and Mamoli's preparations were seriously impure.

TABLE III.

([A] = acetone, [C] = chloroform).

		$[\alpha]_D$.	$[M]_D$.
17*n*-5-*allo*Pregnan-3β-ol-20-one	.....	+ 91° [A] [1], + 96° [C] [2]	+ 290°
17*iso*-5-*allo* ,, ,,	(Calc.)	**− 78°**	− 538
			− 248
17*n*-5-*allo* ,, ,,	acetate	+ 77° [C] [2]	+ 277°
17*iso*-5-*allo* ,, ,,	acetate (Calc.)	**− 78°**	− 538
			− 261
17*n*-5-*allo*Pregnane-3 : 20-dione	.....	+ 121° [A] [1], + 121° [C] [2]	+ 382
17*iso*-5-*allo* ,, ,,	(Calc.)	**− 49°**	− 538
			− 156

[1] Butenandt and Mamoli, *Ber.*, 1935, **68**, 1847.
[2] D. H. R. Barton, private communication.

In order completely to identify the product obtained from substance O diacetate by the Serini reaction, it therefore became necessary to prepare pure specimens of the 17*iso*-ketol and its acetate. This has been accomplished by utilising observations (cf. Gätzi and Reichstein, *Helv. Chim. Acta*, 1938 **21**, 1185, especially 1189) that the configuration at C_{17} has a marked influence on digitonide formation by a 3β-hydroxyl group. It seemed probable that, like its Δ^5-isomeride (Butenandt and Fleischer, *Ber.*, 1937, **70**, 96), the 17*iso*-ketol would not afford an insoluble digitonide despite the presence of a 3β-hydroxyl group, and, in fact, it was possible to find conditions under which the 17*n*-ketol was completely precipitated by digitonin while the 17*iso*-ketol remained in solution.

TABLE IV.

		17*iso*-Ketol.	17*iso*-Acetoxy-ketone.	17*iso*-3 : 20-Diketone.
Synthetic	M. p.	139°	119—122°	148—149°
	$[\alpha]_D$ [E]	− 78° ± 2°	− 75° ± 3°	− 49·5° ± 2·5°
From substance O diacetate	M. p.	139°	118—119°	—
	$[\alpha]_D$ [E]	− 71° ± 4°	− 73° ± 2°	—

The pure 17*n*-ketol, m. p. 193°, $[\alpha]_D$ +89° (in alcohol), was heated with ethanolic potassium hydroxide, and the resulting equilibrium mixture of 17*n*- and 17*iso*-ketols crystallised from

ethanol to remove a portion of the 17*n*-epimeride. The residual material was dissolved in warm 90% ethanol and treated with a warm 2% solution of digitonin in 90% ethanol; after being kept overnight, the precipitate was filtered off, and the material in solution recovered to give, after chromatographic purification, the pure 17*iso*-ketol, which was converted into its acetate and, by oxidation with chromium trioxide in acetic acid at 20°, furnished the pure 17*iso*-3 : 20-diketone. The physical constants of these three substances are set out in Table IV; the m. p. 148—149° for the 17*iso*-3 : 20-diketone has previously been recorded by Marker, Wittle, and Plambeck (*J. Amer. Chem. Soc.*, 1939, **61**, 1333). It will be noted that even hydrolysis of the 17*iso*-acetoxy-ketone with ice-cold potassium hydrogen carbonate appears to lead to traces of the 17*n*-ketol, as indicated by the specific rotation of −71° instead of −78°. Butenandt and Fleischer (*loc. cit.*) were unable to hydrolyse the Δ^5-17*iso*-acetoxy-ketone without causing inversion at C_{17}; in the present case, use of potassium carbonate at 20—25° gave a product, melting at 130—131° to a slightly turbid liquid which cleared at 154°, and having $[\alpha]_D$ −27°, which indicates that inversion to the 17*n*-ketol has occurred to the extent of some 30%.

These results establish the identity of the product obtained from substance O diacetate by the Serini reaction, substantiate the theoretical expectation of inversion of configuration at C_{17}, and so support the view here developed of the mechanism of the Serini reaction.

Experimental.

All m. p.s were determined thermo-electrically on a Kofler block: limit of error ±2°. Solvents for chromatographic analysis were rigorously purified and dried.

3β-*Acetoxy*-17iso-allo*pregnan*-20-*one* (XXV; R = Ac) *from Substance O Diacetate* (VI).—3β : 20α-Diacetoxy*allo*pregnan-17α-ol (substance O diacetate) (m. p. 250—251°; 100 mg.) was heated with zinc dust (1 g.) in toluene [washed with conc. sulphuric acid, dried (Na), and redistilled; 4 c.c.] under reflux with exclusion of moisture and in an atmosphere of nitrogen for 12 hours (bath-temperature 120—125°). The warm solution was filtered, and the excess of zinc well washed with warm acetone (purified through the sodium iodide compound); the filtrate was evaporated completely in a vacuum, and the crystalline residue recrystallised from ether. After this had been washed with ice-cold ether, the following fractions were obtained: (i) long thin prisms, m. p. 225—226°, (ii) thin prisms, m. p. 228—232°, (iii) thin prisms, m. p. 230—244°, and (iv) by evaporation of the final mother-liquor, thin prisms, m. p. 225—243°. Attempted use of acetone–pentane mixtures also failed to give a satisfactory separation of unaltered starting material from the reaction product. The material was reunited (99 mg.) and retreated with zinc (1 g.) in toluene (4 c.c.) as previously, but for 22 hours. The product (98 mg.) was dissolved in benzene (1 c.c.) and introduced onto a column of aluminium oxide (Merck–Brockmann, activity III—IV*; 3 g.) prepared in pentane (15 c.c.). The chromatogram was developed with various eluants (10 c.c.), each eluate (see Table V) being evaporated separately, and the residue crystallised from ether–pentane. In the case of fractions 5 and 6, the crystalline material was washed with pentane.

Table V.

Fraction no.	Eluant.	Eluate.	M. p.
1, 2	Pentane	Traces of oil	—
3, 4	,,	—	—
5	Benzene–pentane (1 : 9)	Oil, cryst. on scratching	110—118°, softening at 105°
6	,, ,, ,,	,, ,,	111—118 , ,, 106
7	,, ,, ,,	Crystallised spontaneously	243—245
8	,, ,, (1 : 4)	,, ,,	246—248
9	,, ,, (1 : 1)	,, ,,	244—247
10	Benzene	,, ,,	245—247
11	Ether–benzene (1 : 9)	,, ,,	242—246
12	,, (1 : 4)	,, ,,	230—242
13	,, (1 : 1)	Traces of oil, could not be induced to crystallise	—
14, 15	Ether	—	—

Fractions 7—12 inclusive were united, and the material (83 mg.), consisting of unchanged starting material, was again treated with zinc dust (1 g.) in boiling toluene (4 c.c.) for 44 hours. The product (80 mg.) was analysed chromatographically using a column of aluminium oxide (Merck–Brockmann; 3 g.) prepared in pentane (see Table VI).

Fractions 5 and 6 of chromatogram 1 (Table V) and 4—14 of chromatogram 2 (Table VI) were united (55 mg.), and the product was subjected to fractionational sublimation at 0·001 mm. The fraction obtained at 90—100° (bath-temperature) consisted of 3β-*acetoxy*-17iso-allo*pregnan*-20-*one* (40 mg.), m. p. (crude) 108—110° with partial transformation into prisms, m. p. 117—118°, $[\alpha]_D^{23°}$ −53° ± 2° (*c*, 1·016 in ethanol); after two crystallisations from methanol, the compound formed prisms, m. p. 118—119°, $[\alpha]_D^{23°}$ −73° ± 2° (after drying at 60°/0·001 mm.; *c*, 1·006 in ethanol) {Found [after sublimation at 100°

* On the scale suggested by Brockmann and Schodder (*Ber.*, 1941, **74**, 73).

bath-temperature)/0·001 mm.]: C, 76·65; H, 9·97. $C_{33}H_{56}O_3$ requires C, 76·62; H, 10·06%}. Over the range 100—140° no sublimate was obtained from the small crystalline residue, but at ~200° this sublimed to give substance O diacetate (10 mg.), m. p. 250° (after recrystallisation from ether–pentane). Allowing for this recovered material, the yield is 46%. The acetate gave no precipitate with a 2% solution of digitonin in 90% ethanol.

3β-*Hydroxy*-17iso-allo*pregnan*-20-*one* (XXV; R = H).—(*a*) The above acetate (20 mg.), dissolved in methanol (3 c.c.), was treated with a solution of potassium carbonate (16 mg.) in water (0·25 c.c.) and set aside for 18 hours at 25°. After complete removal of methanol in a vacuum, and addition of water, the product was filtered off (18 mg.); it appeared to be a hydrate, m. p. ~90°, resolidifying, and remelting at 130—132°. It was fractionally sublimed at 120° (bath-temperature)/0·001 mm.; a portion of the sublimate melted at 130—131° to a turbid melt clearing at 148°. The sublimate was dissolved in ether, the solution concentrated, and, after addition of a little pentane, allowed completely to evaporate; the residual clusters of prisms softened at 125° and melted at 130—131° to a turbid melt clearing at 154°, $[\alpha]_D^{22°}$ −27° ± 3° (*c*, 0·599 in ethanol) [Found (after drying at 60°/0·001 mm.): C, 79·46; H, 10·90. Calc. for $C_{31}H_{54}O_3$: C, 79·20; H, 10·76%]. The product, dissolved in warm 90% ethanol (3 c.c.) and treated with a warm 2% solution of digitonin in 90% ethanol, gave a precipitate rapidly; after the mixture had been kept overnight at 20°, the precipitate was filtered off, well washed with 90% ethanol and with ether, and discarded. The filtrate was evaporated in a vacuum, and extracted with boiling ether (4 × 5 c.c.); the united extracts were filtered and evaporated, to furnish a crystalline residue contaminated with a little oil (9 mg.). This product, dissolved in a minimum of benzene (about 0·25 c.c.), was introduced on to a column of neutralised * aluminium oxide (300 mg.; activity II)

TABLE VI.

Fraction no.	Eluant.	Eluate.	M. p.
1, 2	Pentane	Traces of oil.	—
3	,,	Crystallised by rubbing with pentane.	80— 90°
4	,,	Crystallised after moistening with pentane.	105—115
5	Benzene–pentane (1 : 9)	,, ,, ,, ,,	117
6	,, ,,	,, ,, ,, ,,	118
7	,, ,,	,, ,, ,, ,,	121
8	,, ,,	Crystallised by seeding.	121
9	,, ,,	,, ,,	120
10	,, ,,	,, ,,	118
11	,, (1 : 4)	,, ,,	118
12	,, ,,	,, ,,	120
13	,, (1 : 1)	,, ,,	117
14	,, ,,	,, ,,	123—150 †
15, 16	Benzene	Uncrystallisable oil.	—
17	Ether–benzene (1 : 9)	Traces of uncrystallisable oil.	—
18	,, (1 : 4)	,, ,, ,,	—
19	,, (1 : 1)	,, ,, ,,	—
20	Ether	,, ,, ,,	—
21	Acetone–ether	—	—

† Turbid melt, clearing at 150°.

prepared in pentane (10 c.c.). The column was washed with pentane (5 × 2 c.c.), the last washing leaving no trace of oil on evaporation; elution with benzene–pentane (4 × 2 c.c.) gave diminishing quantities of oil which crystallised when scratched; elution with benzene (2 c.c.) gave a trace of crystalline material, but a second benzene eluate (2 c.c.) gave no appreciable residue on evaporation. The crystalline fractions were united and recrystallised from ether–pentane, to furnish rosettes of prisms, m. p. 139°, resolidifying in stout prisms at 138·5° (4 mg.); the quantity was insufficient for determination of the specific rotation, but the product gave no depression of melting point with a synthetic specimen of 3β-hydroxy-17*iso-allo*pregnan-20-one.

(*b*) The acetate (12 mg.), dissolved in methanol (1·5 c.c.), and a solution of potassium hydrogen carbonate (15 mg.) in water (0·4 c.c.) were mixed and set aside at 20° for 75 hours. After complete removal of methanol in a vacuum at <30° and addition of a little water, the precipitate was filtered off, washed with water until the washings gave no reaction with phenolphthalein, and dried in a desiccator ($CaCl_2$). The product (10 mg.) was crystallised twice from ether–pentane to give rosettes of prisms, m. p. 137—138° after slight softening at 133°, $[\alpha]_D^{21°}$ −71° ± 4° (*c*, 0·488 in ethanol), consisting of almost pure 3β-hydroxy-17*iso-allo*pregnan-20-one.

3β-*Hydroxy*-17iso-allo*pregnan*-20-*one* (XXV; R = H) *from* 3β-*Hydroxy*allo*pregnan*-20-*one* (VII; R = H).—(*a*) A reputed specimen (15 mg.) of the 17*iso*-ketol (XXV; R = H) prepared from the 17*n*-ketol (VII; R = H) by Dr. Barton according to the procedure of Butenandt and Mamoli (*Ber.*, 1935, **68**, 1847) had m. p. 135—157°, $[\alpha]_D^{28°}$ −15° ± 3° (*c*, 0·730 in ethanol). This product (14·3 mg.) was dissolved in warm 90% ethanol (2·5 c.c.) and treated with a warm 2% solution of digitonin in 90% ethanol (2·5 c.c.) and kept overnight at 20°. After filtration from the precipitate, material present in the filtrate was recovered (9·2 mg.) and purified chromatographically on neutralised aluminium oxide as described above. After repeated elution of the column with pentane, use of benzene gave a product which crystallised spontaneously, and, recrystallised from ether–pentane, formed clusters of prisms (4 mg.), m. p. 139°, mixed m. p. 139° with the preparation from substance O diacetate.

* By washing with warm dilute acetic acid and then to neutrality with water, and activated at 200° for 30 hours.

(*b*) The 17*n*-ketol {*allo*pregnanolone (VII; R = H), m. p. 193°, $[\alpha]_D^{20°}$ +89° (EtOH); 970 mg.} was heated with 4% methanolic potassium hydroxide (20 c.c.) under reflux for 2 hours. After addition of a few drops of water, saturation with carbon dioxide, removal of methanol in a vacuum, and addition of water, the precipitate was filtered off and crystallised from ethanol, crystallisation being induced by nucleation with the original specimen; this gave part of the unaltered original material (626 mg.), m. p. 193—194°. The mother-liquor, by complete evaporation in a vacuum, gave a crystalline residue (334 mg.), which was dissolved in warm 90% ethanol (55 c.c.) and treated with a warm 2% solution of digitonin in 90% ethanol (55 c.c.). A precipitate formed in a few minutes, and, after being kept overnight at 20°, was filtered off and well washed with ethanol and with ether. The filtrate was evaporated in a vacuum, and the residue extracted with boiling ether (5 × 20 c.c.) to furnish an oil (159 mg.), which crystallised on keeping overnight. The product, dissolved in benzene (0·5 c.c.), was introduced on to a column of neutralised aluminium oxide (4·8 g.; activity II) prepared in pentane (25 c.c.). The chromatogram was developed as shown in Table VII, each eluate (16 c.c.) being evaporated separately.

TABLE VII.

Fraction No.	Eluant.	Eluate.
1—4	Pentane	Decreasing quantities of oil.
5	,,	—
6	Benzene–pentane (1 : 1)	Trace of oil; no crystallisation by seeding.
7	,, ,,	Oil, crystallised by seeding.
8, 9	,, ,,	Crystallised spontaneously.
10	,, ,,	Crystallised spontaneously whilst hot.
11—14	Benzene	Crystallised spontaneously.
15	Ether–benzene (1 : 9)	Little oil, crystallised by scratching.
16	,, ,,	Traces of oil.

After examination, fractions 8—14 inclusive were united, and the product crystallised from ether–pentane to give 3β-*hydroxy*-17iso-allo*pregnan*-20-*one* (74 mg.) in rosettes of prisms, m. p. 139°, $[\alpha]_D^{22°}$ −77·7° ± 2° (*c*, 1·261 in ethanol), which gave no depression on admixture with the specimen prepared from substance O diacetate [Found (after grinding and drying at 80°/0·001 mm.): C, 79·35; H, 10·90. $C_{21}H_{34}O_2$ requires C, 79·20; H, 10·76%]. The mother-liquor yielded a second crop (5 mg.), m. p. 139°. The compound (5 mg.), dissolved in warm 90% ethanol (1 c.c.) and treated with a warm 2% solution of digitonin in 90% ethanol (1 c.c.), gave no precipitate; after 0·5 hour a faint opalescence was visible, whilst after some hours at 20° only a slight turbidity was observable. The acetate was prepared by dissolving the pure substance (20 mg.) in anhydrous pyridine (0·12 c.c.), adding redistilled acetic anhydride (0·10 c.c.), and allowing the mixture to stand for 16 hours at 20°; after removal of excess of the reagents in a vacuum, the residue was taken up in ether, the etheral solution washed twice with 2N-hydrochloric acid, with dilute ice-cold sodium hydrogen carbonate, and with water, dried (Na_2SO_4), and evaporated, to give a residue which crystallised spontaneously. Recrystallisation from methanol gave 3β-acetoxy-17*iso-allo*pregnan-20-one, prisms, m. p. 119—122°, $[\alpha]_D^{21°}$ −75 ± 3° (after drying at 60°/0·001 mm.; *c*, 0·692 in ethanol) [Found (after drying at 60°/0·001 mm.): C, 76·30; H, 9·80. Calc. for $C_{23}H_{36}O_3$: C, 76·62; H, 10·06%]. A mixture with the specimen prepared from substance O diacetate had m. p. 119—122°, the melt recrystallising on slight cooling to long prisms which remelted at 122°.

17iso-allo*Pregnane*-3 : 20-*dione*.—The 17*iso*-ketol (m. p. 139°, $[\alpha]_D^{22°}$ −77·7°; 25 mg.) was dissolved in acetic acid (redistilled over chromium trioxide; 0·4 c.c.), a 2% solution of chromium trioxide in 98% acetic acid (0·40 c.c.; 8 mg. of $CrO_3 \equiv 1\frac{1}{2}$ atoms of oxygen) added, and the mixture set aside for 16 hours at 20°. After evaporation almost to dryness (bath-temperature, 25—30°/10 mm.), and addition of a little water, the reaction product was extracted with ether; the aqueous solution contained an excess of chromium trioxide. The ethereal extract was washed with 0·01N-sulphuric acid, with ice-cold dilute sodium hydrogen carbonate, and several times with water; the alkaline washing contained an acid oxidation product. The ethereal solution was dried (Na_2SO_4), and evaporated to give a crystalline residue (24 mg.). Recrystallisation from acetone–pentane furnished 17iso-allo*pregnane*-3 : 20-*dione* as prisms, m. p. 148—149°, $[\alpha]_D^{21°}$ −49·5° ± 2·5° (after drying at 60°/0·001 mm.; *c* = 0·808 in ethanol) {Found [after sublimation at 140° (block-temperature)/0·001 mm.]: C, 79·70; H, 9·93. Calc. for $C_{21}H_{32}O_2$: C, 79·70; H, 10·19%}.

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361. *Attempts to find New Spasmolytics. Part VIII. The Synthesis of* 6 : 7-*Diethoxy*-3-*alkyl- and* 6 : 7-*Diethoxy*-3-*phenyl*-isoquinolines.

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A number of 1-substituted 6 : 7-diethoxy-3-ethyl-, -3-propyl-, and -3-phenyl-*iso*quinolines has been synthesized. Except for the 1 : 3-diphenyl compound, all exert similar spasmolytic activity and are more active than papaverine, but none is an appreciable improvement on the 1-phenyl-3-methyl compound.

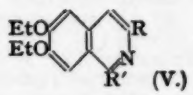
In previous communications (for references see Part VII, *J.*, 1948, 885) we recorded the synthesis of some 1-substituted 3-methyl*iso*quinolines. 3-Methyl*iso*quinolines are effective spasmolytics of low toxicity (Kreitmair, *Arch. exp. Path. Pharm.*, 1932, **164**, 509; cf. B.P. 488,423). Recently a number of 6 : 7-diethoxy-3-methyl*iso*quinolines was prepared (Part VII, *loc. cit.*) and some of these, *e.g.*, the 1-phenyl derivative, were of therapeutic value (Polgár and Zelenka, *Magyar Nógyóyászok Lapja*, 1948, **7**, 1). The methyl group at position 3 of the heterocyclic ring and the two ethoxy-groups in the benzene ring seem to play an important part in the activity and in the low toxicity of these compounds.

In view of these results it was of interest to synthesize 6 : 7-diethoxy-3-ethyl-, -3-propyl-, and -3-phenyl-*iso*quinoline as potentially more effective spasmolytics. We also prepared 6 : 7-diethoxy-3-phenyl-1-methyl*iso*quinoline, to investigate whether an interchange of the methyl and the phenyl radical exerted any influence on the activity.

The route followed was that described in our recent work (*loc. cit.*) :

$$3:4\text{-}(OEt)_2C_6H_3\cdot CO\cdot CH_2R \xrightarrow{} (OEt)_2C_6H_3\cdot CO\cdot CR{:}NOH \xrightarrow{} (OEt)_2C_6H_3\cdot CH(OH)\cdot CHR\cdot NH_2,HCl$$
(I.) (II.) (III.)

$$\xrightarrow{} (OEt)_2C_6H_3\cdot CH(OH)\cdot CHR\cdot NH\cdot COR' \xrightarrow{}$$
(IV.)



(V.)

Experimental.

Ketones (I).—The ketones (I), prepared as described for 3 : 4-diethoxypropiophenone (Part VII, *loc. cit.*), were purified by distillation in a vacuum, and sometimes by recrystallisation from ethanol. M. p.s quoted are those of the recrystallised samples.

3 : 4-*Diethoxybutyrophenone* (I; R = Et). *o*-Diethoxybenzene (33·4 g.), butyryl chloride (21·2 g.), and anhydrous aluminium chloride (28 g.) in nitrobenzene (130 g.) gave the *propyl ketone* (34·5 g., 73%), b. p. 170—175°/5 mm., m. p. 49—49·5° (Found : C, 71·0; H, 8·3. $C_{14}H_{20}O_3$ requires C, 71·2; H, 8·5%).

3 : 4-*Diethoxyvalerophenone* (I; R = Pr^n). *o*-Diethoxybenzene (27·6 g.), valeryl chloride (20 g.), and anhydrous aluminium chloride (23·2 g.) in nitrobenzene (107·7 g.) gave the *butyl ketone* (36 g., 87%), b. p. 170—173°/4 mm., m. p. 45—46° (needles) (Found : C, 72·3; H, 8·9. $C_{15}H_{22}O_3$ requires C, 72·0; H, 8·9%).

3 : 4-*Diethoxy-ω-phenylacetophenone* (I; R = Ph). *o*-Diethoxybenzene (16·6 g.), phenylacetyl chloride (20 g.), and anhydrous aluminium chloride (13·9 g.) in nitrobenzene (64·8 g.) gave the *benzyl ketone* (21 g., 74%), b. p. 206—215°/4—5 mm., m. p. 90—91° (needles) (Found : C, 75·9; H, 7·3. $C_{18}H_{20}O_3$ requires C, 76·0; H, 7·1%).

Oximino-ketones (II).—The ketones were dissolved in dry benzene, and 20% hydrogen chloride in anhydrous ether was added, followed by *iso*butyl nitrite dropwise during 40—65 minutes at 0°. The solution was then stirred at 0° for 90—100 minutes, the crystals were filtered off, and the filtrate was concentrated in a vacuum. A further crop was obtained by washing the residue with light petroleum or benzene. Recrystallisation was from 50—80% alcohol in all cases. Total yields are recorded.

α-Oximino-3 : 4-*diethoxybutyrophenone* (II; R = Et). (I; R = Et) (11·8 g.) in benzene (60 ml.), ethereal hydrogen chloride (20%; 10 g.), and *iso*butyl nitrite (6 g.) gave the *oximino*-compound (11·5 g., 87%) as needles, m. p. 102—103° (Found : C, 63·2; H, 7·3. $C_{14}H_{19}O_4N$ requires C, 63·4; H, 7·2%).

α-Oximino-3 : 4-*diethoxyvalerophenone* (II; R = Pr^n). The ketone (I; R = Pr^n) (12·5 g.) in benzene (100 ml.), ethereal hydrogen chloride (9·1 g.), and *iso*butyl nitrite (5·6 g.) gave the *oxime* (10·5 g., 75%) as yellow needles, m. p. 95—96° (Found : C, 64·8; H, 7·4. $C_{15}H_{21}O_4N$ requires C, 64·5; H, 7·6%).

ω-Oximino-3 : 4-*diethoxy-ω-phenylacetophenone* (II; R = Ph). The ketone (I; R = Ph) (14·2 g.) in benzene (60 ml.), ethereal hydrogen chloride (8·9 g.), and *iso*butyl nitrite (5·5 g.) gave the *oximino-ketone* (12 g., 77%) as yellow needles, m. p. 146° (Found : C, 68·9; H, 6·2. $C_{18}H_{19}O_4N$ requires C, 69·0; H, 6·1%).

Amino-alcohols (III).—These were prepared by Hartung's general method (*J. Amer. Chem. Soc.*, 1931, **53**, 4149; cf. Part VII, *loc. cit.*), involving catalytic reduction of the oximino-ketones in absolute ethanol in the presence of palladised charcoal and hydrogen chloride to the amino-ketone hydrochloride. The excess of hydrogen chloride was then neutralised, and the catalyst and a part of the solvent removed. The amino-ketone salt was further hydrogenated in dilute alcohol with Adams's catalyst to the amino-alcohol hydrochloride which, after removal of water by evaporation, could be crystallised from ethyl

acetate. The period of hydrogenation given is the total for both stages; the yields of amino-alcohols are based on the oximino-ketones reduced.

2-Amino-1-3′ : 4′-diethoxyphenylbutanol hydrochloride (III; R = Et). Reduction of the oximino-ketone (II; R = Et) (10·7 g.) in alcohol (350 ml.) and alcoholic hydrogen chloride (8·9 ml.) in the presence of palladised charcoal (6 g.) and then in 50% alcohol (160 ml.) in the presence of Adams's catalyst (0·7 g.) gave, after 24 hours, the *amino-alcohol hydrochloride* (5·5 g., 47%), m. p. 181—182° (Found: C, 57·7; H, 8·3. $C_{14}H_{23}O_3N$,HCl requires C, 58·0; H, 8·4%).

2-Amino-1-3′ : 4′-diethoxyphenylpentanol hydrochloride (III; R = Pr^n). Reduction of (II; R = Pr^n) (17 g.) in alcohol (200 ml.) and 5N-alcoholic hydrogen chloride (30 ml.) in the presence of palladised charcoal (5 g.) and then in 60% alcohol (260 ml.) in the presence of Adams's catalyst (1 g.) gave the *pentanol* (3·7 g., 20%) as needles, m. p. 192—193° (Found: C, 58·1; H, 8·7. $C_{15}H_{25}O_3N$,HCl,$C_4H_8O_2$ requires C, 58·2; H, 8·7%), containing solvent of crystallisation.

2-Amino-2-phenyl-1-3′ : 4′-diethoxyphenylethanol hydrochloride (III; R = Ph). The ketone (II; R = Ph) was reduced in ethanol (200 ml.) and 5N-alcoholic hydrogen chloride (8 ml.) in the presence of palladised charcoal and then in 80% alcohol (135 ml.) in the presence of Adams's catalyst (0·7 g.). The salt (III; R = Ph) (4 g., 59%) had m. p. 186—187°. The *base*, m. p. 142—143°, was crystallised from benzene (Found: N, 4·8. $C_{18}H_{23}O_3N$ requires N, 4·65%).

Acylamides (IV).—These were prepared as described in Part VII (*loc. cit.*) and recrystallised from dilute alcohol.

Derivatives of (III; R = Et). The amino-alcohol (III; R = Et) (0·5 g.) in water (12 ml.) and benzoyl chloride (0·7 g.) in benzene (6 ml.) gave *2-benzamido-1-3′ : 4′-diethoxyphenylbutanol* (IV; R = Et, R′ = Ph) (0·6 g., 97%), m. p. 158—159° (Found: C, 70·4; H, 8·1. $C_{21}H_{27}O_4N$ requires C, 70·6; H, 7·7%). The *phenylacetamide* (IV; R = Et, R′ = CH_2Ph) (1·2 g., 97%), m. p. 143—145°, was prepared from (III; R = Et) (1 g.) in water (18 ml.) and phenylacetyl chloride (0·7 g.) in benzene (7 ml.) (Found: C, 70·9; H, 7·9. $C_{22}H_{29}O_4N$ requires C, 71·1; H, 7·9%). The *3″ : 4″-dimethoxybenzoyl* derivative [IV; R = Et, R′ = 3 : 4-$C_6H_3(OMe)_2$] was obtained from (III; R = Et) (1 g.) in water (10 ml.) and 3 : 4-dimethoxybenzoyl chloride (0·8 g.) in benzene (8 ml.); yield, 1·3 g. (90%); m. p. 154—155° (Found: C, 65·2; H, 8·2. $C_{23}H_{31}O_6N$ requires C, 66·1; H, 7·5%).

Derivatives of (III; R = Pr^n). *2-Benzamido-1-3′ : 4′-diethoxyphenylpentanol* (IV; R = Pr^n R′ = Ph), m. p. 162—163°, was prepared from (III; R = Pr^n) (0·8 g.) in water (30 ml.) and benzoyl chloride (0·15 ml.) in benzene (5 ml.) (Found: C, 71·0; H, 8·0. $C_{23}H_{29}O_4N$ requires C, 71·1; H, 7·8%). The ON-*bisphenylacetyl* derivative (IV; R = Pr^n, R′ = CH_2Ph) was made from (III; R = Pr^n) (0·8 g.) in water (30 ml.) and phenylacetyl chloride (0·8 g.) in benzene (6 ml.); yield, 71% (0·94 g.); m. p. 140—141° (Found: C, 73·3; H, 7·5. $C_{31}H_{37}O_5N$ requires C, 73·9; H, 7·4%). The *3″ : 4″-dimethoxybenzoyl* derivative [IV; R = Pr^n, R′ = 3 : 4-$C_6H_3(OMe)_2$] was obtained from (III; R = Pr^n) (0·8 g.) in water (30 ml.) and 3 : 4-dimethoxybenzoyl chloride (0·8 g.) in benzene (6 ml.); yield, 1·12 g. (98%); m. p. 164—165° (Found: C, 68·0; H, 7·8. $C_{24}H_{33}O_6N$ requires C, 68·8; H, 7·7%).

Derivatives of (III; R = Ph). *2-Benzamido-2-phenyl-1-3′ : 4′-diethoxyphenylethanol* (IV; R = R′ = Ph) was prepared from (III; R = Ph) (1·5 g.) in water (60 ml.) and benzoyl chloride (2 ml.) in benzene (6 ml.); yield, 1·5 g. (85%); m. p. 214—215° (Found: C, 73·7; H, 6·8. $C_{25}H_{27}O_4N$ requires C, 74·1; H, 6·7%). The *acetyl* derivative (IV; R = Ph, R′ = Me) was prepared from the alcohol (1 g.) in dry pyridine (20 ml.) and acetic anhydride (0·6 ml.) at 20°; yield, 1 g. (90%); m. p. 171—172° (Found: C, 69·7; H, 7·5. $C_{20}H_{23}O_4N$ requires C, 69·9; H, 7·3%).

iso*Quinolines* (V).—The following *iso*quinolines were obtained by boiling the acylamides in toluene with an excess of phosphoryl chloride for an hour (Part VII, *loc. cit.*). The yields quoted refer to the free bases, which were recrystallised from 50% alcohol. *6 : 7-Diethoxy-1-phenyl-3-methyl*isoquinoline (75·5% yield), m. p. 100—101°, from (IV; R = Et, R′ = Ph) (Found: C, 78·7; H, 7·1. $C_{21}H_{23}O_2N$ requires C, 78·5; H, 7·2%); *6 : 7-diethoxy-1-benzyl-3-ethyl*isoquinoline (44% yield), m. p. 88—89°, from (IV; R = Et, R′ = CH_2Ph) (Found: C, 78·0; H, 7·7. $C_{22}H_{25}O_2N$ requires C, 78·8; H, 7·5%); *6 : 7-diethoxy-1-3′ : 4′-dimethoxyphenyl-3-ethyl*isoquinoline (66% yield), m. p. 98—99°, from [IV; R = Et, R′ = 3 : 4-$C_6H_3(OMe)_2$] (Found: C, 69·0; H, 7·2. $C_{23}H_{27}O_4N,H_2O$ requires C, 69·2; H, 7·3%); *6 : 7-diethoxyphenyl-3-propyl*isoquinoline (52% yield), m. p. 94—95°, from (IV; R = Pr^n, R′ = Ph) (Found: N, 4·2. $C_{22}H_{23}O_2N$ requires N, 4·3%); *6 : 7-diethoxy-1-benzyl-3-propyl*isoquinoline (48% yield), m. p. 107—108°, from (IV; R = Pr^n, R′ = CH_2Ph) (Found: C, 78·9; H, 8·3. $C_{23}H_{27}O_2N$ requires C, 79·1; H, 7·8%); *6 : 7-diethoxy-1-3′ : 4′-dimethoxyphenyl-3-propyl*isoquinoline (48·5% yield), m. p. 90—91°, from [IV; R = Pr^n, R′ = 3 : 4-$C_6H_3(OMe)_2$] (Found: N, 3·9. $C_{24}H_{29}O_4N$ requires N, 3·5%); *6 : 7-diethoxy-1 : 3-diphenyl*isoquinoline (44% yield), m. p. 173—174°, from (IV; R = R′ = Ph) (Found: C, 80·9; H, 7·8. $C_{25}H_{23}O_2N$ requires C, 81·3; H, 7·3%); and *6 : 7-diethoxy-3-phenyl-1-methyl*isoquinoline (50% yield), m. p. 137—138°, from (IV; R = Ph, R′ = Me) (Found: C, 78·1; H, 6·8. $C_{20}H_{21}O_2N$ requires C, 78·3; H, 6·9%).

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362. *Fluorescence Spectra of Polycyclic Aromatic Hydrocarbons in Solution.*

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The approximate mirror-image relation between the fluorescence spectrum of a compound and the bands of longest wave-length of its ultra-violet absorption spectrum, already observed in a number of cases, has been found to hold for a series of polycyclic aromatic hydrocarbons and some related compounds. In each case the fluorescence band of shortest wave-length was found to occupy approximately the same position as the longest absorption band. Regularities previously observed in the long-wave region of ultra-violet absorption spectra (cf. Braude, *Ann. Reports*, 1945, **42**, 105) have been found to apply to the fluorescence spectra of derivatives of polycyclic aromatic hydrocarbons.

Comparison of the fluorescence spectra of isomeric hydrocarbons, with different arrangements of the rings, has shown a correlation between the position of the spectrum and the number of quinonoid rings in the structure with the maximum number of Kekulé rings, *i.e.*, the structure which conforms to the Fries rule. Fluorescence spectra have been used in the elucidation of structure of derivatives of partly reduced polycyclic aromatic hydrocarbons.

Fluorescence spectra have already been extensively used in the identification of polycyclic aromatic hydrocarbons and their derivatives, particularly in relation to biological problems (for references, see Berenblum and Schoental, *J.*, 1946, 1017). However, by comparison with ultra-violet absorption spectroscopy relatively little use has been made of the much simpler fluorescence spectroscopy, especially in regard to the relations between spectra and chemical constitution. Fluorescence is to some extent the reverse of absorption. It reflects energy changes which accompany the return of a π electron from the lowest vibrational level of the excited state to different vibrational levels of the ground state. Such a transition of a π electron which has remained in the excited state for about 10^{-8} second gives rise to a set of fluorescence bands. The constant spacing between them corresponds to the energy differences of the vibrational levels of the *ground* state, whereas the spacing of bands in the *absorption* spectra corresponds to the vibrational energy levels of the *excited* state (cf. Bowen, *Quart. Reviews*, 1947, **1**, 1).

Few quantitative measurements of the fluorescence spectra of aromatic compounds have been recorded hitherto. Of these, the spectrum of benzene has received most attention (*e.g.*, Henri, *J. Phys. Radium*, 1922, **3**, 181; Ingold and Wilson, *J.*, 1936, 941); it is very complicated, on account of the peculiar symmetry of this hydrocarbon. The reproductions of photographs of fluorescence spectra, recorded by small dispersion spectrographs, which have usually been published, are not suitable for accurate photometric examination. The degree of accuracy of fluorescence data depends on the sharpness of the bands. Not only is this a characteristic of some electronic transitions, but it is also associated with the state of " fluorescence purity " of the specimen. The criteria of purity for fluorescence spectrography are different from those for other purposes. Thus, small traces of strongly fluorescent impurity may completely vitiate the fluorescence spectrum of the compound, and care must be taken to exclude even weakly fluorescent impurity. On the other hand, contamination with non-fluorescent materials is usually of little importance. The fact that compounds of similar structure exhibit fluorescence spectra of similar pattern furnishes a useful guide to the reliability of the spectra. Thus, the persistence of a subsidiary set of bands in the spectra of a number of naphthofluorenes (Table I), prepared by different types of method, indicates that these bands are a characteristic feature of the spectra of hydrocarbons of this character.

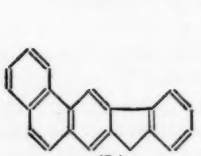
The specimens used in the present investigation were mostly samples which had been purified for elementary analysis, although some were submitted also to chromatography. The sharpness of the bands varied widely, however, and an accuracy of greater than ± 50—100 cm.$^{-1}$ is not claimed for the photometer readings. Data marked in the tables with an asterisk are regarded as falling below this standard. With some of the compounds examined it was not practicable to make quantitative intensity measurements, owing to low solubility or the minute amounts available. Very dilute solutions in light petroleum were employed. In a few cases the solubility in this solvent was too slight, and then benzene or liquid paraffin was used. The concentrations used were just sufficient to give the strongest bands of the fluorescence spectra, and, although some weaker bands may have been missed, this procedure avoided the risk of reabsorption due to overlap of fluorescence and absorption spectra with its attendant shift to the red of the first band (Sannié, *Biochem. J.*, 1936, **30**, 704; Bowen, *loc. cit.*). Precautions to exclude " oxygen

quenching" were not taken, as we were concerned mainly with the positions of the bands rather than their absolute intensities.

TABLE I.†

Compound.	Fluorescence maxima, $V' \times 10^{-3}$. (A.)	(B.)	Absorption maximum of lowest wave-number, $V' \times 10^{-3}$. (C.)	Ref.	$(V'_a - V'_f) \times 10^{-3}$. (D.)
Naphtho(2′ : 1′-2 : 3)fluorene (I) *	276 262 248	269 254	—	—	—
Naphtho(1′ : 2′-1 : 2)fluorene (II) *	275 261 247	269	—	—	—
Naphtho(1′ : 2′-2 : 3)fluorene (III)	274 260 246	267 253	275·5	1	+1·0
Naphtho(2′ : 1′-1 : 2)fluorene (IV)	273 259 245	266	274	4	+1·0
5-Methyl ,, ,, ...	272·5 258·5 244·5	267 253	—	—	—
6-Methyl- ,, ,, ...	272·0 258·0 244·5	265 251	—	—	—
7-Methyl- ,, ,, ...	271·0 257·5 244·0	265 251	—	—	—
8-Methyl- ,, ,, ...	272·5 258·5 244 *	265 251	—	—	

* For the synthesis of these compounds see Cook and Stephenson, this vol., p. 842.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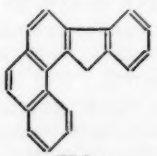
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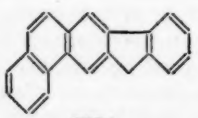
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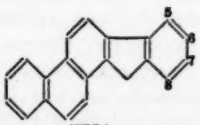


(IV.)

The spectra examined ranged from 31,000 to 16,000 cm.$^{-1}$. Although the positions of the fluorescence maxima are independent of the wave-length of the excited radiation, the intensity of fluorescence depends on the extinction coefficient and the intensity of the exciting radiation. The mercury line at 3650 A. was used where possible, but in certain cases, indicated in the tables, it was necessary to use radiations of other wave-lengths for excitation.

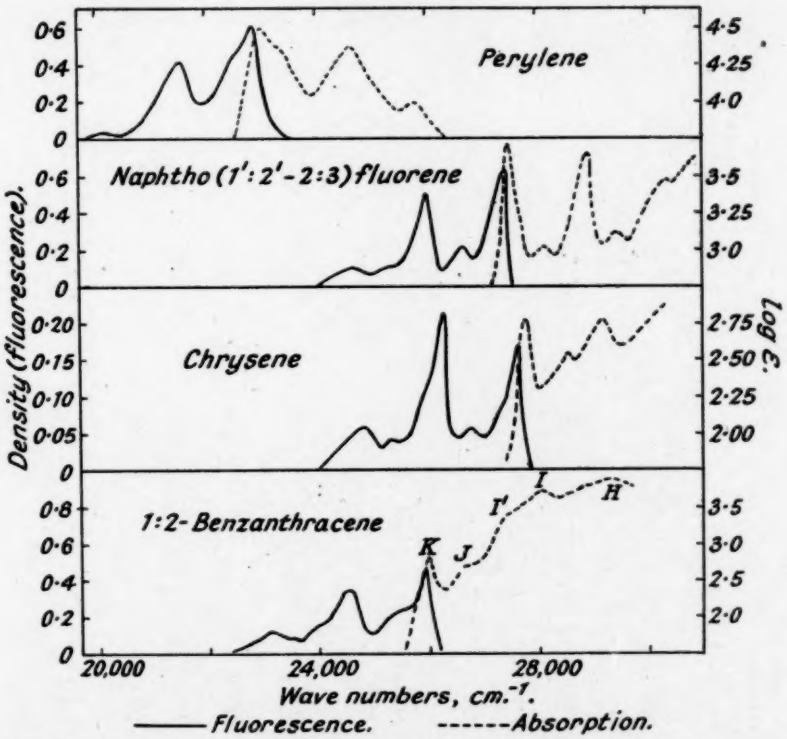
Discussion of Results.

(a) *General.*—As may be seen from Fig. 1 and Tables I to VII, the fluorescence spectra of polycyclic aromatic hydrocarbons in solution are relatively simple. They consist usually of one main set of 3—4 bands of diminishing intensity, equally spaced at about 1400 cm.$^{-1}$ and accompanied sometimes by a second interwoven set of equally-spaced, less intense, subsidiary bands. This second set of bands is associated usually with hydrocarbons containing angularly-condensed benzene rings. Thus, in the spectrum of anthracene, as in that of naphthacene, the maximum intensity almost coincides with the centre of the bands (slight duplication of the bands was observed in the anthracene spectrum by Sambursky and Wolfsohn, *Trans. Faraday Soc.*, 1940, **36**, 427, and Kortüm and Finkh, *Z. physikal. Chem.*, 1942, *B*, **52**, 263); but with 1 : 2-benzanthracene the subsidiary bands appear as inflections on the longer slopes of the main bands (Fig. 1), whereas in the cases of chrysene, 1 : 2 : 5 : 6-dibenzanthracene, and the naphthofluorenes they appear as distinct bands.

† For references and explanations of symbols used in Tables I—VI see p. 1696. For significance of asterisks see p. 1683.

Fig. 1 gives the fluorescence spectra of representative hydrocarbons, dissolved in light petroleum, together with their ultra-violet absorption bands of longest wave-length.* The absorption data, taken from the literature, were obtained usually in alcoholic solution. In general, the approximate mirror-image relation between the fluorescence and the absorption spectra (Lewschin, *Z. Physik*, 1931, **72**, 368, 382) is quite striking. In some cases, *e.g.*, with

FIG. 1.



Comparison of fluorescence spectra with the corresponding longest wave-length bands of the respective ultra-violet absorption spectra.

1 : 2-benzanthracene, this is somewhat obscured by the superposition in the absorption spectrum of additional bands which probably belong to another electronic transition. The absorption bands corresponding with the second and third fluorescence bands then appear only as inflexions. In cases of this kind comparison of the two spectra may assist in identifying the bands of the more complex absorption spectrum which are due to a particular electronic transition.

Tables II and III give the frequencies of the maxima of the fluorescence bands of a number of polycyclic aromatic hydrocarbons. The main system is given in column *A* and the subsidiary system in column *B*. For comparison, the frequency of the maximum of the longest absorption band, where it is known, is given in column *C*. Groups of isomeric hydrocarbons are tabulated together. The shortest fluorescence band is seen to coincide with the longest absorption band with a deviation not exceeding −300 cm.$^{-1}$ (Tables II and III; column *D*). This deviation, although small, is probably greater than the limits of experimental error and greater even than the differences to be attributed to the use of different solvents for the two types of spectra (compare Seshan, *Trans. Faraday Soc.*, 1936, **32**, 689, and Sambursky and Wolfsohn, *Phys. Review*, 1942, **62**, 357).† Hausser, Kuhn, and Kuhn (*Z. physikal. Chem.*, 1935, *B*, **29**, 417)

* In the figures and the tables wave-numbers are used, but for convenience reference is made in the text to wave-lengths. The expression "longest absorption band" is used to denote the ultra-violet absorption band of longest wave-length.

† The absence from the absorption spectrum of 1 : 2 : 6 : 7-dibenzpyrene of a band corresponding to the first fluorescence band may be due to the fact that absorption bands of lower intensity than log $\varepsilon = 2{\cdot}5$ are not recorded for this compound.

TABLE II.

Compound.	Exciting radiation.	Fluorescence maxima, $V' \times 10^{-2}$. (A.)	(B.)	Absorption maximum of lowest wave-number, $V' \times 10^{-2}$. (C.)	Ref.	$(V'_a - V'_f) \times 10^{-2}$. (D.)	$\Delta V'_f \times 10^{-2}$. (E.)	Number of quinonoid rings. (Q.)	Number of Kekulé resonance structures. (K.)	Carcinogenicity.
Naphthalene (V)	2_7 [a]	310 300 289 *	307 297 * 286 *	313·5	2, 4	+3·5	—	0	3	—
Phenanthrene (VI)	2_1 [a]	288 274·5 261 *	280 266	289·9	2, 4	+1·9	—	0	5	—
Anthracene (VII)	3	265 250·5 236·5 223 *	—	267·8	3, 4	+2·8	23	1	4	—
Triphenylene (VIII)	2_2 [a]	283 *	—	285·5	2	+2·5	−6·5	0	9	—
Chrysene (IX)	2	276·5 262·5 248	268 253	278	2, 4	+1·5	—	0	8	—
1 : 2-Benzanthracene (X)	3	259·5 245·5 231	—	260	3, 4, 5	+0·5	17·0	1	7	—
Naphthacene (XI)	3	212 197·5	—	211 [b]	3	−1·0	64·5	2	5	—
3 : 4 : 5 : 6-Dibenzphenanthrene (XII)	2_1 [a]	266 *	—	—	—	—	−2	0	13	—
Picene (XIII)	3	264 [b] 250·5 237·0	256 243	266 [c]	4	+2·0	—	0	13	—
Naphtho(2′ : 3′-1 : 2)phenanthrene (XIV)	3	255·5	—	254·5 [b]	2	−1·0	8·5	1	11	—
1 : 2 : 7 : 8-Dibenzanthracene (XV)	3	253·5	—	253 [b]	6	−0·5	10·5	1	12	±
1 : 2 : 5 : 6-Dibenzanthracene (XVI)	3	254·0 240·0 225·5	246	253·0	4, 7	−1·0	10·0	1	12	++

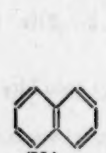
Naphtho(2′ : 3′-2 : 3)phenanthrene (XVII)	3	222·0 208·0 194·0	—	221 [b]	2	−1·0	42·0	2	9	—
Pentacene (XVIII)	54	173 *[f]	—	172·5 [b]	8	−0·5	91·0	3	6	—
1 : 2 : 3 : 4 : 5 : 6-Tribenzanthracene (XIX)	3	257·5 244 * 230 *	(263)	257·5 [b]	9	0·0	—	1	22	—
Phenanthro(3′ : 2′-2 : 3)phenanthrene (XX)	3	230 215 201	—	231	10	1·0	—	2	16	—

* Subscript refers to exposure time in hours; 54 = 5461 A. For explanation of 2 and 3 see Experimental.

[b] Solution in benzene.

[e] Solution in chloroform.

[f] Solution in liquid paraffin.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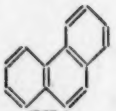
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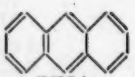
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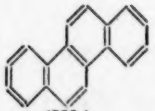
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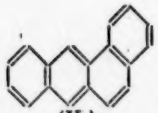
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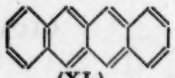
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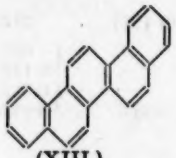
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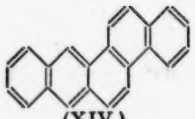
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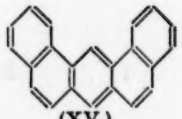
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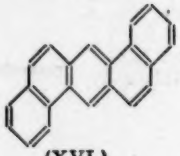
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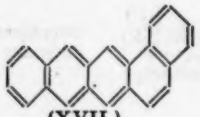
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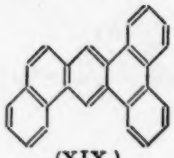
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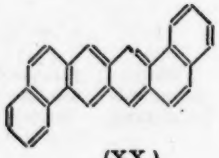
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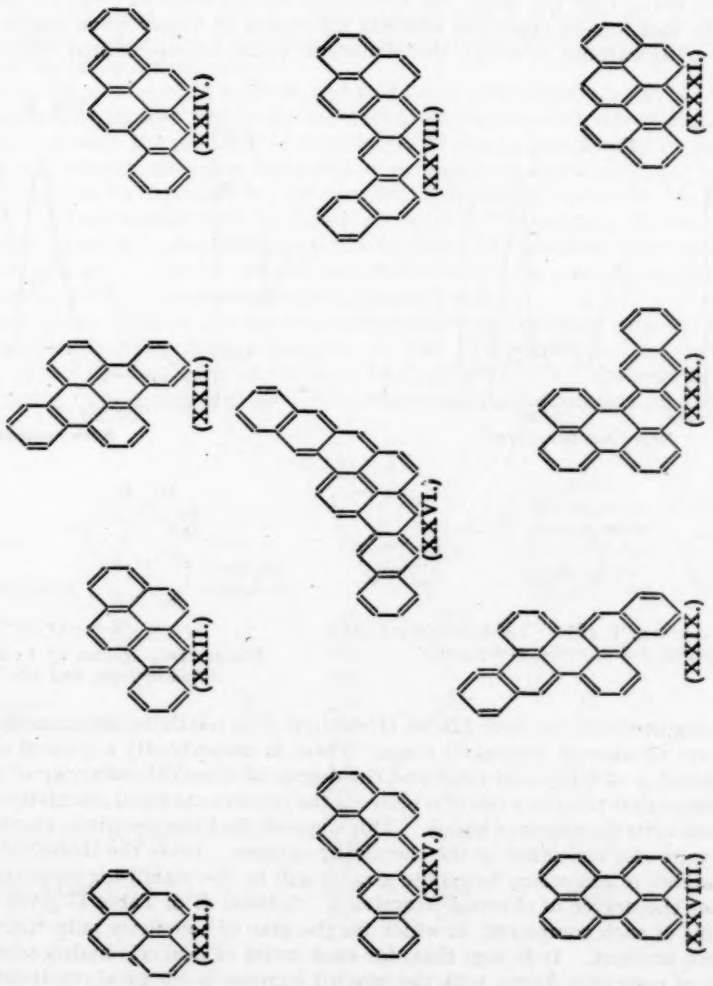
TABLE III.

Compound.	Exciting radiation.	Fluorescence maxima, $V'_f \times 10^{-2}$. (A.)	(B.)	Absorption maximum of lowest wave-number, $V'_a \times 10^{-2}$. (C.)	Ref.	$(V'_a - V'_f) \times 10^{-2}$. (D.)	Number of Kekulé resonance structures. (K.)	Number of quinonoid rings. (Q.)	Carcino-genicity.
Pyrene (XXI)	2	268·5 264 261 258 255 *	—	269·5	11	1·0	6	1	—
3 : 4-Benzpyrene (XXII)	3	248·0 234·0 220·5	245·0 232·0 241·0 229	248·0	4	0·0	9	1	+++
1 : 2 : 6 : 7-Dibenzpyrene (XXIII)	3	253·0 239·0 225·5	246	(261·5) [b]	12	—	20	1	—
3 : 4 : 8 : 9-Dibenzpyrene (XXIV)	3	223·0 209·5	—	221·5 [b]	11	−1·5	13	2	+++
Naphtho(2′ : 3′-3 : 4)pyrene (XXV)	3	219 205 191	—	218·5 [b]	11	−0·5	12	2	—
Dinaphtho(2′ : 3′-3 : 4)(2″ : 3″-9 : 10)pyrene (XXVI)	3	194 180 167	187	—	—	—	26	3	—
Phenanthro(3′ : 2′-3 : 4)pyrene (XXVII)	3	229·5 214·5 200 *	—	—	—	—	21	2	—
Perylene (XXVIII)	3	228·5 215 201	—	230	13	1·5	9	1	—
2 : 3 : 8 : 9-Dibenzperylene (XXIX)	3	231 217	—	230·5 [b]	14	−0·5	25	1	—
Naphtho(2′ : 3′-1 : 2)perylene (XXX)	57 [a]	163 * [l]	—				15	3	
Anthanthrene (XXXI)	3	232·5 219	229	231 [b]	15	−1·5	10	2	—

[a] Exciting radiation, 5770 A. [b] Solution in benzene. [l] Solution in liquid paraffin.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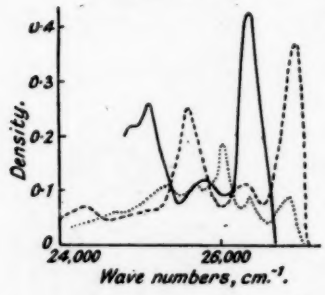
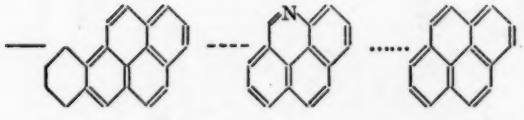
studied the relation between fluorescence and absorption spectra of a series of diphenylpolyenes and found the deviation of the coincident bands to increase with the nunber of double bonds. No such regularity was observed in our series of hydrocarbons. The spacings between the main bands of the fluorescence spectra are constant within the limits of experimental error, being about 1400 cm.$^{-1}$. The spacings between the bands of the subsidiary systems are also the same, but with different compounds the two systems are shifted with respect to one another.

According to Fries's rule the arrangement of double bonds in the molecules of polycyclic aromatic hydrocarbons should be such as to lead to Kekulé structures for the maximum number of rings, with a corresponding minimum number of quinonoid rings. We have observed a relation between this minimum number of quinonoid rings and the positions of the fluorescence bands. It was found that the larger the number of such quinonoid rings in the molecule the greater was the shift of the spectrum towards the region of longer wave-length, as compared with isomeric hydrocarbons of which the structures could be represented entirely by Kekulé

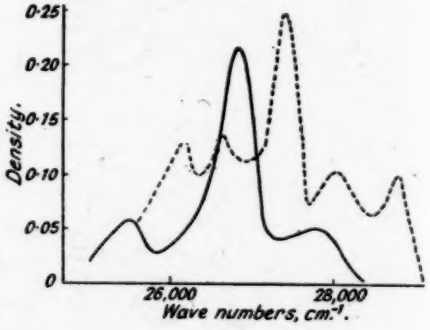
FIG. 2.

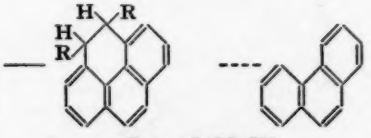




Fluorescence spectra of 1′ : 2′ : 3′ : 4′-*tetrahydro*-3 : 4-*benzpyrene*, 1-*azapyrene, and pyrene.*

FIG. 3.





R = -O·CO·CH$_3$.

Fluorescence spectra of 1 : 2-*diacetoxy*-1 : 2-*dihydropyrene and phenanthrene.*

forms. The magnitude of this shift (Table II, column *E*) is related approximately to the square of the minimum number of quinonoid rings. There is undoubtedly a general correspondence between this number of quinonoid rings and the degree of chemical reactivity of the compound, and hence it seems that there is a relation between the relative chemical reactivity of a compound and the position of its fluorescence bands. This suggests that the electronic transitions reflected in fluorescence are also concerned in the chemical reactions. From the theory of resonance, the greater the number of resonance forms the greater will be the stabilising resonance energy, and hence the lower the degree of chemical reactivity. Column *K* of Table II gives the number of resonance forms of each compound, in which for the sake of simplicity only Kekulé forms have been taken into account. It is seen that, for each series of isomeric hydrocarbons, a decrease in the number of resonance forms, with the implied increase in chemical reactivity, is associated with a shift of the fluorescence spectrum towards the red. Evidently the position of the spectrum is not the only criterion of chemical reactivity, for, if we consider the series of hydrocarbons, anthracene, 1 : 2-benzanthracene, and 1 : 2 : 5 : 6-dibenzanthracene, all of which contain a minimum of one quinonoid ring, the fluorescence spectra are seen to be shifted progressively towards the red as the number of rings increases, whereas the chemical reactivity diminishes. Possibly this last phenomenon is connected with steric inhibition at the *meso*-positions.

(b) *Hydrocarbons with Highly Condensed Ring-systems.*—The spectrum of pyrene (Table III; Fig. 2) consists of five narrow bands of close proximity and unequal spacing. The complexity of this spectrum suggested contamination of the specimen. However, the spectrum produced

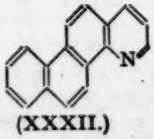
by a sample of pyrene from coal-tar was in no way different from that given by a sample isolated from products of petroleum cracking and purified exhaustively by chromatography, vacuum-sublimation, and recrystallisation. This spectrum closely resembled those already recorded for pyrene (Hieger, *Biochem. J.*, 1930, **24**, 505; Miescher *et al.*, *Biochem. Z.*, 1936, **287**, 189). The complexity of the spectrum is probably due to the high degree of molecular symmetry. The curves published by Förster and Wagner (*Z. physikal. Chem.*, 1937, **37**, *B*, 353) show that in the absorption spectrum of 4-methylpyrene there is a similar series of closely packed bands, but in the spectrum of the unsymmetrical 3-methylpyrene some of these bands were less prominent or absent. We have found that with other unsymmetrical derivatives of pyrene, such as 1-azapyrene and 1′ : 2′ : 3′ : 4′-tetrahydro-3 : 4-benzpyrene (Fig. 2) there were also simplification of the pattern and modification of the spacing of the fluorescence bands. Thus the conclusion of Berenblum and Schoental (*loc. cit.*) that substitution does not materially affect the pattern of fluorescence spectra of the parent hydrocarbons seems invalid when a high degree of molecular symmetry is destroyed by substitution.

Comparison of the spectra of 1 : 2 : 6 : 7- and 3 : 4 : 8 : 9-dibenzpyrenes and of naphtho(2′ : 3′-3 : 4)pyrene (Table III) showed that in the two last cases there is a considerable shift to the red. This is in agreement with the presence of a minimum of one quinonoid ring in the structure of the first compound, whereas the other two substances must have two such rings. Also the order of chemical reactivities, as expressed by the number of resonance forms (20, 13, 12) (Table III, column *K*) is in good agreement with the observed shifts of the spectra. It may be noted also that, whilst the number of quinonoid rings seems to define the position of the spectrum, within broad limits, the number of possible Kekulé structures reflects the amounts of the smaller shifts observed in isomers with the same number of quinonoid rings.

The positions of the bands in the spectrum of perylene do not agree with the structure with four Kekulé benzenoid rings usually assigned to this hydrocarbon. The simplicity of the spectrum (Fig. 1) and the frequency of the main band (22830 cm.)$^{-1}$ * are more in accord with a structure containing two quinonoid rings. Two examples of more complex perylene derivatives

TABLE IV.

Compound.		Exciting radiation.	Fluorescence maxima, $V' \times 10^{-3}$. (*A.*)	(*B.*)	Main fluorescence maximum of corresponding hydrocarbon, $V'_{Hom.} \times 10^{-3}$.	$(V'_{Het.} - V'_{Hom.}) \times 10^{-3}$.
6-Azachrysene.....	(XXXII)	2	276·5 262 248	269 254	276·5	0
6-Aza-3 : 4-benzphenanthrene	(XXXIII)	2	268 255·5 243	263 250	—	—
1-Azapyrene.....	(XXXIV)	2	269 255 242	263 249	268·5	+0·5
1 : 2 : 5 : 6-Dibenzacridine	(XXXV)	2	253·5 240	247	254·0	−0·5
3 : 4 : 5 : 6-Dibenzacridine	(XXXVI)	3	255 241 228	248 235	253·5	+1·5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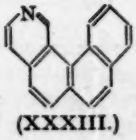
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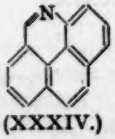
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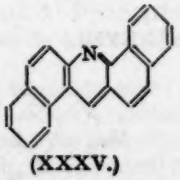
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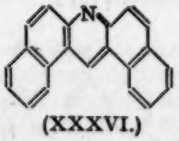

(XXXVI.)

* A similar value was obtained with an alcoholic solution by Seshan (*loc. cit.*). The position of the first band recorded by Ganguly (*Indian J. Physics*, 1944, **19**, 347) shows considerable displacement towards the red. Unequal spacing of the bands suggests that this displacement is due to concentration quenching.

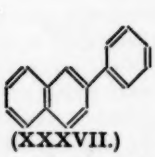
are naphtho(2′ : 3′-1 : 2)perylene * (having 15 resonance structures) and 2 : 3 : 8 : 9-dibenzperylene (with 25 resonance structures). The fluorescence spectrum of the highly reactive naphthoperylene showed the expected shift towards the region of longer wave-length, whereas the spectrum of 2 : 3 : 8 : 9-dibenzperylene was shifted somewhat towards the region of shorter wave-length, as compared with perylene itself, with the same number of quinonoid rings (cf. Clar, *Ber.*, 1932, **65**, 846).

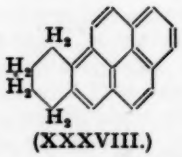
(c) *Aza-compounds.*—It is well known that replacement of a =CH– group of an aromatic ring by the isoelectronic nitrogen atom does not greatly influence the ultra-violet absorption spectrum of a compound. Hence it is not to be expected that the position of the fluorescence bands would

TABLE V.

Compound.	Exciting radiation.	Fluorescence maxima, $\nu'_f \times 10^{-3}$. (A.)	(B.)
2-Phenylnaphthalene (XXXVII)	2_1 *	292 *	289 *
		279 *	
		264 *	
1′ : 2′ : 3′ : 4′-Tetrahydro-3 : 4-benzpyrene (XXXVIII)	2	263	257
		250	
1 : 2-Diacetoxy-1 : 2-dihydropyrene (XXXIX)	2	279 * §	—
		269	
		255	
1 : 2-Diacetoxy-1 : 2-dihydrochrysene (XL)	2	289 §	284 *
		275 *	268 *
		262 *	254 *
3 : 4-Diacetoxy-3 : 4-dihydro-1 : 2-benzanthracene (XLI; R = H)	2	287 §	—
		274	
		262 *	
6 : 7-Diacetoxy-6 : 7-dihydro-3 : 4-benzpyrene (XLII)	2	272 §	—
		258	
		244 *	
Diacetoxy-5 : 9 : 10-trimethyldihydro-1 : 2-benzanthracene (XLI; R = Me)	2	280 * §	—
		268 *	
6 : 7-Diacetoxy-20-methyl-7 : 6-dihydrocholanthrene (XLIII; R = OAc)	2	280 §	—
		267	
		253 *	
20-Methyl-6 : 7-dihydrocholanthrene (XLIII; R = H)	2	284 §	—
		270 §	
		256	
3 : 4-Diacetoxy-3 : 4-dihydro-1 : 2 : 5 : 6-dibenzanthracene (XLIV)	2	271 §	—
		257	
		243 *	
5-Ethyl-7 : 8-dihydro-1 : 2-benzanthracene (XLV)	3	273	—
		259	
		245 *	

* Exposure time, hours. § Solution in benzene; others in light petroleum.


(XXXVII.)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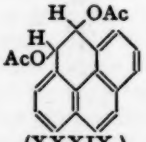
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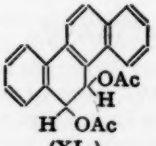
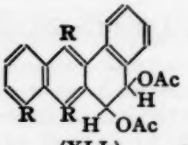
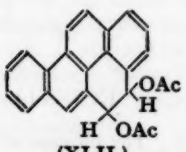
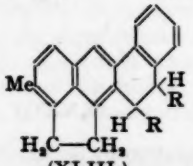

(XL.)


(XLI.)


(XLII.)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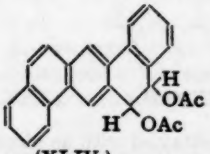
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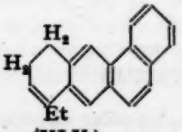
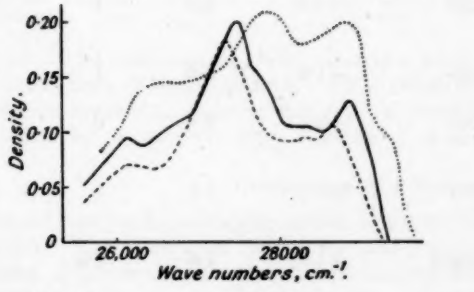

(XLV.)

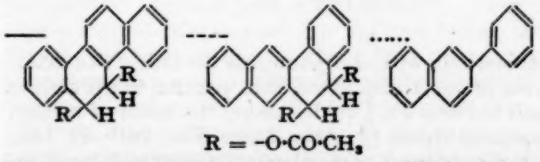
* Synthesised by Clar and Wright by a method not yet published.

be greatly affected, and this was found to be the case, although the intensity of fluorescence was considerably augmented. Thus, the fluorescence spectra of two dibenzacridines closely resembled those of the corresponding dibenzanthracenes (Table IV), and the same parallelism holds for chrysene and the corresponding 6-azachrysene. The case of pyrene and 1-azapyrene has already been discussed (Fig. 2 and Table IV).

(d) *Hydroaromatic Compounds.*—The approximate mirror-image relation between fluorescence and absorption spectra suggested the use of the former for identification of hydroaromatic compounds in appropriate cases. Compounds formed by partial hydrogenation of fused-ring aromatic compounds are difficult to free from the more intensely fluorescent, purely aromatic compounds, but the diacetates of the diols formed by oxidation of polycyclic aromatic hydrocarbons with osmium tetroxide (Cook and Schoental, *J.*, 1948, 170) provided convenient test materials (see Table V and Figs. 2, 3, 4, and 5). The fluorescence spectrum of 1 : 2-diacetoxy-1 : 2-dihydropyrene showed, as was to be expected, the main characteristics of that of phenanthrene, but is shifted towards the red by about 500 cm.$^{-1}$. The spectra of 1 : 2-diacetoxy-1 : 2-dihydrochrysene and 3 : 4-diacetoxy-3 : 4-dihydro-1 : 2-benzanthracene both resemble that of 2-phenylnaphthalene, with a shift towards the red. On account of the additional

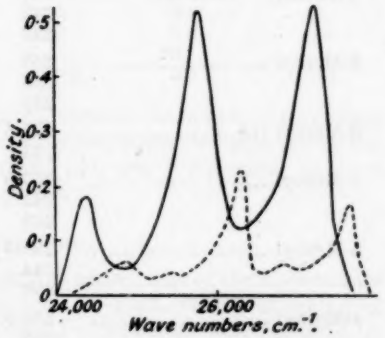
FIG. 4.

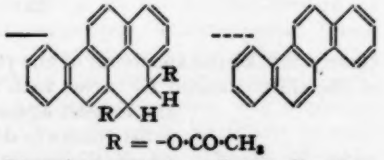




Fluorescence spectra of 1 : 2-*diacetoxy*-1 : 2-*dihydrochrysene*, 3 : 4-*diacetoxy*-3 : 4-*dihydro*-1 : 2-*benzanthracene, and* 2-*phenylnaphthalene.*

FIG. 5.





Fluorescence spectra of 6 : 7-*diacetoxy*-6 : 7-*dihydro*-3 : 4-*benzpyrene and chrysene.*

substitution, 3 : 4-diacetoxy-5 : 9 : 10-trimethyl-3 : 4-dihydro-1 : 2-benzanthracene showed a greater displacement towards the region of longer wave-length. This spectrum is similar to that of the corresponding diacetate prepared from 20-methylcholanthrene, which may therefore be assumed to be the 6 : 7-diacetoxy-6 : 7-dihydro-compound. The spectrum of this likewise resembles that of 6 : 7-dihydro-20-methylcholanthrene, except that in the latter case the spectrum is displaced towards the region of shorter wave-length. The spectrum of the diacetate from 1 : 2 : 5 : 6-dibenzanthracene resembles that of naphtho(1′ : 2′-2 : 3)fluorene, which indicates that the diacetoxy-groups have been added to the 3 : 4-positions. This was confirmed chemically by oxidation to the known 1 : 2 : 5 : 6-dibenz-3 : 4-anthraquinone (Cook, *J.*, 1933, 1594).

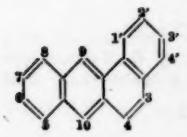
In the case of 3 : 4-benzpyrene the attack by osmium tetroxide might conceivably take place at the 1 : 2- or the 6 : 7-positions. The former would lead to a residual 1 : 2-benzanthracene system, the latter to a residual chrysene system. The spectrum resembled that of chrysene, but with a shift of 450 cm.$^{-1}$ towards the red, indicating that oxidation had occured at the 6 : 7-positions. The spectrum of 5-ethyl-7 : 8-dihydro-1 : 2-benzanthracene is of interest as it lies between those of phenanthrene and 1 : 2-benzanthracene.

(e) *Homologues of* 1 : 2-*Benzanthracene.*—The fluorescence spectra of nine of the twelve possible monomethyl-1 : 2-benzanthracenes are recorded in Table VI. The patterns resemble

TABLE VI.

Compound.	Fluorescence maxima, $V'_f \times 10^{-2}$. (*A.*)	Absorption maximum of lowest wave-number, $V'_a \times 10^{-2}$. (*C.*)	$(V'_a - V'_f) \times 10^{-2}$. (*D.*)	$\Delta V'_f \times 10^{-2}$. (*E.*)	$\Delta V'_a \times 10^{-2}$. (*F.*)	Carcinogenicity.
1 : 2-Benzanthracene (XLVI)	259·5 245·5 231	260	+0·5	—	—	—
Derivatives thereof :						
9-Methyl	254 240 *	254·5 *	+0·5	5·5	5·5	++
10-Methyl	256 242 229	257	+1·0	3·5	3	++
3-Methyl	256·5 243 229	—	—	3·0	—	+
1′-Methyl	257 243 230	258	+1·0	2·5	2	—
8-Methyl	257 243 229	259	+2·0	2·5	1	—
6-Methyl	257·5 243 *	259	+1·5	2·0	1	+
7-Methyl	257·5 243 229	260	+2·5	2·0	0	+
5-Methyl	258·5 244 230	259	+0·5	1·0	1	++
4-Methyl	258·5 245 230	259·5	+1·0	1·0	0·5	+

closely that of the spectrum of the parent hydrocarbon, with shifts towards the red. The extent of the shift (column *E*) varies with the position of substitution and runs parallel to the shift of the longest absorption band (column *F*). In discussing the effect of methyl substituents in different positions, Jones (*J. Amer. Chem. Soc.*, 1940, **62**, 148; *Chem. Reviews*, 1943, **32**, 1) emphasised particularly the shift exhibited by another band (band *H*; cf. Fig. 1), which was shifted to the greatest extent in the case of 10-methyl-1 : 2-benzanthracene. It would appear, however, that band *K*, equivalent to the shortest fluorescence band, is of greater importance, and this shows the greatest shift in the case of 9-methyl-1 : 2-benzanthracene. The next largest shifts are shown by the 10-methyl and then the 3-methyl isomers. It may be of significance that these are the most reactive positions of the unsubstituted molecule, position 10 being much more reactive than position 9, possibly on account of steric hindrance at the latter position. It is of interest also that in their most recent calculations, using the method of molecular orbitals, Berthier, Coulson, Greenwood, and Pullman (*Compt. rend.*, 1948, **226**, 1906) assigned the highest value for the free valency index to position 9. Their calculated values for other positions do not, however, correlate with the shift in fluorescence spectrum caused by methyl substitution at those positions.



(XLVI.)

The fluorescence spectra of seven dimethyl-1 : 2-benzanthracenes have been examined (Table VII). Substitution at both *meso*-positions led to a remarkably large shift, which was followed by that for the 5 : 6-dimethyl compound. Substitution in the β-positions of the benzanthracene system seemed to have little effect, and even caused shifts towards the region of shorter wave-length. Thus, whereas the shift to the red of the benzanthracene spectrum was 200 cm.$^{-1}$ in the case of the 6- and 7-monomethyl derivatives, it was only 150 cm.$^{-1}$ with the 6 : 7-dimethyl compound. Higher-alkyl groups at position 5 of the benzanthracene molecule produced shifts of the spectrum not appreciably different from that caused by methyl. This is seen in Table VII, which gives also the effect of substituents other than alkyl groups at position

TABLE VII.

Compound.	Fluorescence maxima of main bands, $V'_f \times 10^{-3}$.			Shift of first band from that of (XLVI), $\Delta V'_f \times 10^{-3}$.	Carcinogenicity.
1 : 2-Benzanthracene (XLVI)	259·5	—	—	—	—
Derivatives thereof :					
2′ : 6-Dimethyl	257·5	243	229	2·0	—
2′ : 7-Dimethyl	255·5	242	228	4·0	—
3′ : 6-Dimethyl	258·0	243	230	1·5	—
3′ : 7-Dimethyl	257·5	243	229	2·0	—
5 : 6-Dimethyl	253 *	—	—	6·5	++
6 : 7-Dimethyl	258·0	244	230	1·5	+
9 : 10-Dimethyl	247 *	—	—	12·5	+++
5-Ethyl	259	245	230	0·5	+
5-*n*-Propyl	258·5	245	230	1·0	+
5-*iso*Propyl	258·5	245	230	1·0	+
5-Phenyl	256·5	243 *	—	3·0	±
5-Carboxy	249 *	—	—	10·5	—
10-Acetoxymethyl	256·5	243	229	3·0	+
10-Ethoxymethyl	257	243	229	2·5	+
10-Hydroxymethyl	256·5	243	229	3·0	+
10-Cyano	252·0	238	225	7·5	—
4′-Amino	237 *	—	—	22	
4′-Methoxy	254	240	226·5	5·5	—

5 and 10. The cyano-group, with its triple bond conjugated with an aromatic ring, caused larger shifts than did alkyl groups. Polar substituents also have considerable influence on the fluorescence spectrum, causing not only a considerable shift, but also diffuseness. This is exemplified by 5-carboxy- and 4′-amino-1 : 2-benzanthracenes.

Comparison of Fluorescence Intensities.

In a few cases sufficient material was available for quantitative assessment of the fluorescence intensities. The method of Berenblum and Schoental (*Biochem. J.*, 1942, **36**, 86) of matching intensities of bands on photographic plates was used, but visual estimations were replaced by photometric readings (see Experimental). Comparison was made of the similar spectra of closely related compounds. In the case of two nitrogenous compounds (6-azachrysene, 1-azapyrene), the intensities were about 10 times as great as those of the related hydrocarbons. The fluorescence intensities of three isomeric pentacyclic hydrocarbons, each containing one quinonoid ring in its structure [1 : 2 : 7 : 8-dibenzanthracene, 1 : 2 : 5 : 6-dibenzanthracene, and naphtho-(2′ : 3′-1 : 2)phenanthrene], were in the ratio 1 : 10 : 300. The amount of variation in such closely related compounds is noteworthy. It should be stated that, on account of weak intensities, long exposures were required and diffuse spectra were obtained with triphenylene, 3 : 4 : 5 : 6-dibenzphenanthrene, and 1 : 2 : 7 : 8-dibenzanthracene; consequently, only approximate positions of the maxima of one main band are recorded for the spectra of these compounds and of those of the photolabile pentacene and naphtho(2′ : 3′-1 : 2)perylene.

The fluorescence intensity of 3 : 4 : 8 : 9-dibenzpyrene is about six times that of 1 : 2 : 6 : 7-dibenzpyrene, but as the positions of the spectra differ they are not strictly comparable. The exceedingly intense fluorescence of perylene could be recorded with a 3-minutes' exposure in a concentration of 0·1 μg. per ml. It may be noted that there is no direct relation between the carcinogenic activity of some of the compounds and the position or intensity of the fluorescence spectrum.

EXPERIMENTAL.

Fluorescence Spectra in the Region 31,000—25,000 *cm.*$^{-1}$ (3000—4000 A.).—Radiation from a mercury-vapour lamp S (Kelvin, Bottomley, and Baird), enclosed in a black box, was condensed by a 500-ml. silica flask containing a 10% solution of nickel sulphate ($NiSO_4,7H_2O$). This filter absorbed the mercury lines at 3650 and 4047 A., excitation being effected mainly by the 2537—2650 A. group, designated as 2 in the tables. A reduced image of the lamp was formed about 5 mm. from the slit of a Hilger medium quartz spectrograph (slit, 0·1 mm.) which was inclined at 80° to the path of the light. At the slit of the spectrograph was placed a quartz cell (1 × 1 cm.) containing the solution to be examined. Exposures varied usually from 5 to 15 minutes, but were as long as several hours in specific cases which have been mentioned. Ilford Special Rapid plates were used.

Fluorescence Spectra in the Region 27,000—22,000 *cm.*$^{-1}$ (3700—4500 A.).—Radiation from a 250-watt Mazda Compact Source Mercury Lamp was condensed by two quartz lenses (focal lengths, 6″ and 8″) and then passed through a Wood's filter. The excitation radiation (3650—3663 A.) is designated as 3

in the tables. An image of about 3 mm. in height was formed close to the spectrograph, oriented as described in the preceding paragraph. Exposures were about 3 minutes. Ilford Panchromatic plates were used.

Fluorescence Spectra in the Region 25,000—17,000 *cm.*$^{-1}$ (4000—6500 A.).—Radiation from the same source as recorded in the preceding paragraph was used, but the Wood's filter was replaced by appropriate glass filters so as to give the green or yellow mercury light.* The quartz spectrograph was replaced by a Hilger medium glass spectrograph. Exposures, lasting from 3 to 10 minutes, were made on Ilford Panchromatic plates.

Procedure.—Solutions of the compounds in redistilled light petroleum (b. p. 60—80°) were prepared and the concentrations adjusted by visual observation in ultra-violet light so that there was no appreciable quenching. A number of spectra was photographed on the same plate, interspersed with mercury emission spectra to facilitate measurements. The positions of the bands were measured using a Hilger microphotometer (slit, 0·2 mm.). The plate was initially oriented in the holder so that the mercury lines on each side of the fluorescence spectra were correctly aligned. Measurements were made every 0·5 mm. from the ultra-violet edge of one of the mercury lines (3342 or 3650 A.) until the whole spectrum had been traversed. For accurate determinations, readings were taken every 0·05 mm. near the heads of the bands. From a distance calibration table, obtained from an iron-arc spectrum, the wave-lengths of the heads of the bands could be obtained.

When the glass spectrograph was used, a wave-length scale was imprinted above and below each spectrogram. Microphotometric readings were taken every 20 A. For accurate readings, the distance of the head of the band from a line on the scale was measured, and the wave-length then found by interpolation.

To measure the density of the bands, a reading was taken initially of an unexposed part of the plate. The resistance in series with the photocell was adjusted so that this reading corresponded to the maximum deflection on the scale (50 cm.). Readings were then taken as already described and the logarithms of the values so obtained were subtracted from $\log_{10} 50$. Density curves were obtained by plotting $\log_{10}$ density against wave-numbers.

Quantitative comparisons of fluorescence intensities were made by matching the intensities of spectrograms produced by serial dilution of the compound under examination with that of a standard solution of 3 : 4-benzpyrene, photographed on the same plate under standardised conditions. The ratio of the concentrations required to give the same photographic density was taken as an inverse measure of the relative fluorescence intensities.

Tables.—References to ultra-violet absorption spectra in Tables I, II, III, IV, and VI are: (1) Mayneord and Roe, *Proc. Roy. Soc.*, 1937, *A*, **158**, 634; (2) Clar and Lombardi, *Ber.*, 1932, **65**, 1411; (3) Clar, *ibid.*, p. 503; (4) Mayneord and Roe, *Proc. Roy. Soc.*, 1935, *A*, **152**, 299; (5) Jones, *J. Amer. Chem. Soc.*, 1940, **62**, 148; (6) Clar, "Aromatische Kohlenwasserstoffe," Berlin, 1941, p. 147; (7) Clar and Lombardi, *Gazzetta*, 1932, **62**, 539; (8) Clar, *Ber.*, 1936, **69**, 607; (9) Clar, "Aromatische Kohlenwasserstoffe," Berlin, 1941, p. 148; (10) Nichol *et al.*, *J. Amer. Chem. Soc.*, 1947, **69**, 376; (11) Clar, *Ber.*, 1936, **69**, 1671; (12) *Ber.*, 1943, **76**, 609; (13) *Ber.*, 1932, **65**, 846; (14) *Ber.*, 1932, **65**, 846; cf. Schanenstein, and Bürgermeiser, *Ber.*, 1943, **76**, 208; (15) Clar, *Ber.*, 1940, **73**, 596.

Unless otherwise specified, the solutions used were in light petroleum (b. p. 60—80°), and the exciting radiation was 3650 A. ν' denotes wave-number in cm.$^{-1}$.

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363. *The Ethoxyfluorosilanes.*

By H. J. EMELÉUS and H. G. HEAL.

A rapid disproportionation of diethoxydichlorosilane into the mono- and the tri-ethoxy-compound has been observed. *Ethoxytrifluorosilane* has been prepared by reaction of the corresponding chloro-compound with antimony trifluoride. It disproportionates at room temperature. Triethoxyfluorosilane can be prepared from triethoxychlorosilane and antimony trifluoride and is stable up to 100°. Diethoxydifluorosilane exists at room temperature only in equilibrium with the mono- and the tri-ethoxy-compound.

THE ethoxychlorosilanes $SiCl_3{\cdot}OEt$, $SiCl_2(OEt)_2$, and $SiCl(OEt)_3$ were first described by Friedel and Crafts (*Ann. Chim. Phys.*, 1863, **9**, 11) but the fluorine analogues of these compounds were unknown until recently. A brief report of their preparation by the fluorination of the chloro-compounds was published by Heal (*Nature*, 1946, **158**, 672). Peppard, Brown, and Johnson (*J. Amer. Chem. Soc.*, 1946, **68**, 76) have also prepared di- and tri-ethoxyfluorosilane by the reaction of ethyl orthosilicate with antimony trifluoride and antimony pentachloride.

* Designated in the tables as 54 and 57, respectively.

They failed, however, to observe the disproportionation of diethoxydifluorosilane, and this communication, beside describing an alternative preparative method and some of the physical properties of these compounds, clarifies the question of their disproportionation.

Friedel and Crafts (*loc. cit.*) described the three ethoxychlorosilanes as stable substances which had definite boiling points, and were obtained by heating mixtures of ethyl orthosilicate and silicon tetrachloride in the molecular proportions 1 : 3, 1 : 1, and 3 : 1. Pellini, however, stated that the products of these reactions could not be separated by distillation (*Gazzetta*, 1915, **45**, 380). In an attempt to repeat this preparation of diethoxydichlorosilane, the product, when distilled, has been found to consist largely of the mono- and the tri-ethoxy-compound, which boiled at the temperatures given by Friedel and Crafts. The middle fraction, on repeated distillation, resolved itself progressively into the last two derivatives according to the equation $2SiCl_2(OEt)_2 \rightleftharpoons SiCl_3{\cdot}OEt + SiCl(OEt)_3$. With rapid distillation, using an efficient column, it is probable that diethoxydichlorosilane would show a definite boiling point, and the discrepancy between the results of Friedel and Crafts and of Pellini may be due to different conditions of distillation. A similar explanation may be given for the fact that Peppard, Brown, and Johnson (*loc. cit.*) were able to isolate diethoxydifluorosilane whereas the experiments described below show that this substance disproportionates readily.

Ethoxytrifluorosilane was prepared from antimony trifluoride and the corresponding chloro-compound, from which it differed by showing a ready disproportionation at room temperature. The product of this reaction contained silicon tetrafluoride and other ethoxyfluorosilanes and was purified by fractional condensation in a Stock vacuum apparatus. The disproportionation probably occurred according to the equation $2SiF_3{\cdot}OEt \rightleftharpoons SiF_3(OEt)_2 + SiF_4$. The diethoxy-compound is itself unstable (see below) and, at equilibrium, only about one-third of the monoethoxy-compound is decomposed. The boiling point of ethoxytrifluorosilane, extrapolated from vapour-pressure data, is about −7°, the vapour-pressure equation being $\log p = 8{\cdot}17 - 1400/T$. The latent heat of vaporisation is 6400 cals./mol., Trouton's constant 24·1, the melting point −122°, and the liquid density at −63° 1·32 g./c.c. An uncertainty occurs in the vapour-pressure data because of the possibility of slow disproportionation in the liquid.

Since it had proved impossible to prepare diethoxydichlorosilane as an intermediate, the preparation of di- and tri-ethoxyfluorosilanes was attempted by treating triethoxychlorosilane with antimony trifluoride, when it was thought that some of the diethoxy-compound would be formed by disproportionation. From the mixture of products in this reaction two fractions (b. p. 70—110° and 110—145°) were distilled off at atmospheric pressure. The first of these probably contained an unstable diethoxydifluorosilane, the boiling point of which is given by Peppard, Brown, and Johnson as 83—83·5°. These authors did not observe the disproportionation of the diethoxy-compound, probably because their material was distilled only once through a long column. In the vacuum apparatus, however, six successive fractional condensations of a sample of the 70—110° fraction each yielded a mixture of the mono- and tri-ethoxy-compounds. In each operation the amount of each of these two compounds formed was about one-eighth of the total material treated. This amount did not diminish in relation to the main fraction with successive distillations. It was concluded that diethoxydifluorosilane changes quickly, after condensation, into an equilibrium mixture containing roughly three parts of diethoxydifluorosilane and one part of the mixed mono- and tri-ethoxy-derivatives. The analytical results for the final " diethoxydifluorosilane " condensate were approximately those for the pure compound, a result which is consistent with the presence of the two disproportionation products.

Pure triethoxyfluorosilane was isolated without difficulty by high-vacuum fractionation of the 110—145° fraction : it was condensed out at −40° and was a colourless liquid which fumed in moist air, was immediately hydrolysed by water to form gelatinous silica, and burnt with a luminous flame. The boiling point at 760 mm. was found by extrapolation of the vapour-pressure graph to be 134·6°, in reasonable agreement with the value given by Peppard, Brown, and Johnson (133—133·5°). The vapour-pressure equation was $\log p = 8{\cdot}040 - 2104/T$, the latent heat of vaporisation was 9620 cals./mol., and Trouton's constant 23·8. The compound set to a transparent glass when cooled, and its melting point was not determined. The vapour-pressure curve of a sample kept at 100° for 1 hour was completely unchanged, showing that the rate of disproportionation at this temperature is inappreciable.

The physical properties of the ethoxyfluorosilanes resemble closely those of the corresponding ethylfluorosilanes (Emeléus and Wilkins, *J.*, 1944, 454). The latter, however, do not disproportionate and are more resistant to hydrolysis : triethylfluorosilane, for example, is

unattacked by cold water whereas the triethoxy-derivative is immediately hydrolysed. The tendency to disproportionate is greater in the ethoxyfluoro- than in the ethoxychloro-compounds. A further point of interest is that no catalyst is required for the reactions between antimony trifluoride and the ethoxychlorosilanes, whereas the reaction between antimony trifluoride and silicon tetrachloride does not occur unless a quinquevalent antimony compound is present. Fluorination of either of the stable ethoxychlorosilanes yields a mixture of the three ethoxyfluorosilanes, showing a partial breakdown of the C–O–Si bond system. Fluorination does not affect the C–Si bonds in the ethyl chlorosilanes (Emeléus and Wilkins, *loc. cit.*) but it largely disrupts the Si–O–Si bonds in hexachlorodisiloxane (Booth and Osten, *J. Amer. Chem. Soc.*, 1945, **67**, 1092).

Experimental.

Ethoxytrichlorosilane and Triethoxychlorosilane.—It was intended to prepare each of the ethoxychlorosilanes separately, but the ready disproportionation of the diethoxy-compound, when its preparation was attempted, provided a method of obtaining the other two. Half-molar quantities of redistilled ethyl orthosilicate and silicon tetrachloride were mixed and heated in Carius tubes for three hours at 150°. The contents of the tubes were then distilled through an 8″ column. There were well-marked arrests in the rise of b. p. at 103° and 155°, the b. p.s given by Friedel and Crafts for mono- and tri-ethoxychlorosilanes, but no arrest at 136°, which is given as the boiling point of diethoxydichlorosilane. The middle fraction, which would contain the last compound, resolved itself into higher- and lower-boiling fractions in subsequent distillations, and after three successive distillations of the middle fraction the following quantities of the various products were isolated: $SiCl_3{\cdot}OEt$, b. p. 102·5—104°, 31 g.; $SiCl_2(OEt)_2$, b. p. 136—138°, 4 g.; $SiCl(OEt)_3$, b. p. 154—156·5°, 48 g. A second preparation gave practically the same results.

Fluorination of Ethoxytrichlorosilane.—Antimony trifluoride was well dried in a vacuum desiccator before use. The silane (30 g.) was added at the rate of about one drop per second to a 50% excess (45 g.) of antimony trifluoride in a bulb with a sealed-in tap-funnel. The bulb was continually shaken. The temperature rose to about 70° and the reaction mixture liquefied. The volatile products were led off through a water-cooled condenser to a trap cooled in liquid air, a stream of dry nitrogen being passed throughout the reaction. After the reaction, the contents of the low-temperature trap were pumped into the fractionating line of a Stock vacuum apparatus. *Ethoxytrifluorosilane* (Found: Si, 22·9, 21·2; F, 43·5, 42·0. $EtOSiF_3$ requires Si, 21·5; F, 43·8%) was isolated by keeping the reaction product at a temperature at which the vapour pressure was 2—5 mm. and allowing the vapour to pass through a series of three traps in the vacuum apparatus kept at −80°, −110°, and −185°. The first removed less volatile ethoxyfluorosilanes, the monoethoxy-compound separated at −110°, and silicon tetrafluoride passed into the −185° trap. It was characterised by vapour-pressure measurements.

Preliminary experiments showed that the disproportionation of ethoxytrifluorosilane was fairly rapid at room temperature, but was inappreciable below about −20°. In the above method of separation decomposition of the liquid at −110° would be negligible, and the main source of contamination of the product was the decomposition during the vapour-pressure determinations. In measuring the vapour pressure of the compound, the sample was contained in a large bulb which was wholly immersed in the cooling bath and connected by a capillary to an external mercury manometer. In this way only the small amount of vapour in the capillary was at room temperature and readings were fairly steady. Temperatures were measured with an ammonia vapour pressure thermometer. The following data were obtained:

Temp.	−66·7°	−62·0°	−56·5°	−51·5°	−48·4°	−44·7°	−36·6°	−30·8°	−25·3°
V. p., mm.	19	34	49	68	85	105	178	253	315

The m. p. determined by Stock's method (" The Hydrides of Boron and Silicon," p. 184) was −122° ± 1°. The liquid density of ethoxytrifluorosilane was measured by distilling a sample into a pyknometer at −63°, which was sealed off from the vacuum system and weighed. The volume at room temperature was determined by filling with mercury, correction being made for the expansion of the glass in calculating the density at −63°.

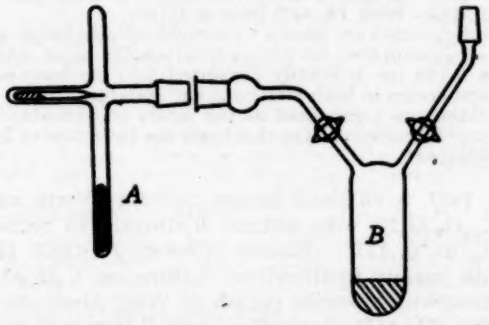
Fluorination of Triethoxychlorosilane.—Triethoxychlorosilane (30 g.) was mixed with a 60% excess of antimony trifluoride in a Kon flask, which was cooled in water while the reaction proceeded and then left to stand for some time. All products boiling up to 170° were distilled off at atmospheric pressure. The distillate was redistilled from a further 5 g. of antimony trifluoride, fractions boiling at 70—110° and 110—145° being collected. In both distillations gaseous products escaped. The two fractions were separately subjected to fractional condensation in the vacuum apparatus. In the case of the 70—110° fraction, which was believed to contain diethoxydifluorosilane, condensing traps at −30°, −75°, and −185° were used, the diethoxy-compound being removed at −75°. Unlike the monoethoxy-compound, which could be resubmitted to fractional condensation without appreciable condensates appearing in the traps at −80° or −185°, the diethoxy-compound when refractionated gave both mono- and tri-ethoxy-fractions, the proportions of which have already been mentioned. These substances reappeared in each fresh distillation and were formed at the temperature (*ca.* 0°) at which the substance was vaporised in order to submit it to fractional condensation in the low-temperature traps. The final " diethoxydifluorosilane " condensate had nearly the same analytical composition as pure diethoxydifluorosilane [Found: Si, 16·8; F, 23·6. Calc. for $SiF_2(OEt)_2$: Si, 18·0; F, 24·3%].

Triethoxyfluorosilane [Found: Si, 15·6, 16·0; F, 10·3, 10·1. Calc. for $SiF(OEt)_3$: Si, 15·4; F, 10·4%] was obtained without difficulty by high-vacuum fractionation of the 110—145° fraction. It was condensed out at −40°, with neighbouring traps at −10° and −185°. There was no evidence of

disproportionation in this case. Vapour-pressure measurements were made with an isoteniscope, temperatures being measured with a standard mercury thermometer. Data are recorded below:

Temp.	17·6°	40·0°	60·1°	70·0°	79·2°	89·0°	100·7°
V. p., mm.	6·5	21	53	81	116	169	255

Analysis.—Silicon and fluorine were determined on the same sample. Each sample (0·2—0·4 g.) was distilled into a short, thin-walled weighing tube, which was sealed off from the vacuum system with a capillary neck. A file scratch was made at the base of this capillary, and the tube with its sample was weighed. The capillary was broken off in a special capillary-breaker (see figure, *A*), in which a



weighted glass rod fell on to the capillary when the breaker was rotated on its ground joint. During this operation the capillary-breaker was evacuated and in communication with the hydrolysis bulb *B*, which contained potassium hydroxide solution (100% excess over that required to hydrolyse the sample), frozen in liquid air. The sample distilled on to the hydrolysing agent at once. The stopcock between hydrolysis bulb and capillary breaker was closed, and the bulb warmed in boiling water until the gelatinous silica at first precipitated had dissolved. The empty weighing tube and its capillary were weighed.

The hydrolysate was washed out of the bulb, and 4 g. of ammonium carbonate were added. After 24 hours most of the silica had separated, and was filtered off, washed with water, and dried. The filtrate was evaporated on a steam-bath, to decompose excess of ammonium carbonate. 3 C.c. of ammoniacal zinc oxide solution were added, and evaporation continued until the solution no longer smelled of ammonia. The precipitate of zinc oxide and silicate was filtered off, washed, and dissolved in a little concentrated hydrochloric acid. This solution was evaporated to dryness, and the residue baked at 130° for several hours. More acid was added, and the evaporation and baking repeated. After three such operations, the now insoluble silica was moistened with dilute hydrochloric acid, filtered off, washed, and dried. It was combined with the main silica precipitate, and ignited and weighed, to give the silicon content of the sample.

The fluoride in the filtrate from the zinc oxide precipitation was precipitated in a mixture of calcium fluoride and carbonate by adding a solution of 5 g. of hydrated calcium nitrate. The mixed precipitate was treated by the classical gravimetric procedure for fluorine analysis, the carbonate being removed by evaporations with acetic acid. After weighing, the calcium fluoride was converted into calcium sulphate, and this weighed as a check. The weights agreed well in all cases.

Disproportionation of Ethoxytrifluorosilane.—The following figures illustrate the disproportionation of this silane. 0·3694 G. of the purified compound was distilled into a 60-c.c. gas-weighing bulb, which was then left at room temperature for 18 hours: as judged from the speed of disproportionation observed, this time should have amply sufficed to allow the substance to come to equilibrium with its disproportionation products. The liquid did not vaporise quite completely. The pressure in the bulb was about one atmosphere. The entire contents of the bulb were then fractionally condensed in a series of traps at −75°, −120°, and −185°, so separating them into crude diethoxydifluorosilane, ethoxytrifluorosilane, and silicon tetrafluoride fractions. The middle fraction was redistilled in the same way, and the resulting −75° and −185° fractions combined with those first obtained. The combined −185° (silicon tetrafluoride) fraction was redistilled to remove a little ethoxytrifluorosilane, which was added to the main ethoxytrifluorosilane fraction. All fractions were then weighed, giving:

SiF_4	0·0592 g.	(−185°)
$SiF_3{\cdot}OEt$	0·2225 g.	(−120°)
Heavy fraction [mainly $SiF_2(OEt)_2$]	0·0865 g.	(−75°)
Total	0·3682 g.	(99·7% recovery)

Calculation shows the composition of the heavy fraction to have been approximately $SiF_{1\cdot9}(OC_2H_5)_{2\cdot1}$. It probably consisted mainly of diethoxydifluorosilane, with some triethoxyfluorosilane.

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364. *The* Senecio *Alkaloids. Part III. The Structure of Retrorsine and Isatidine, and the Isomerism of Retronecic Acid and Isatinecic Acid.*

By Stuart M. H. Christie, Meyer Kropman, Ernest C. Leisegang, and Frank L. Warren.

Retronecic and isatinecic acids, previously obtained by hydrolysis of retrorsine and isatidine, respectively, have now each been obtained from both these alkaloids; retronecic acid is identical with "new" isatinecic acid obtained by de Waal (*Onderstepoort J. Vet. Sci. Animal Husb.*, 1939, **12**, 155; 1940, **14**, 445) from isatidine.

Isatinecic and retronecic acids are shown to contain an ethylidene group and are, respectively, *cis*- and *trans*-$\alpha\beta$-unsaturated dihydroxy-dicarboxylic acids which on reduction give identical dihydro-acids. The *cis*- is readily converted into the *trans*-isomer and it is in the *cis*-form in which the acid occurs in both retrorsine and isatidine.

Retrorsine and isatidine are formulated as the esters of isatinecic acid with retronecine and retronecine *N*-oxide, respectively. On this basis the reduction of isatidine to octahydroanhydroisatidine is explained.

Manske (*Canad. J. Res.*, 1931, **5**, 651) and Barger, Seshadri, Watt, and Yabuta (*J.*, 1935, 11) hydrolysed retrorsine, $C_{18}H_{25}O_6N$, with sodium hydroxide to retronecine, $C_8H_{13}O_2N$, and retronecic acid, $C_{10}H_{16}O_6$, m. p. 177°. Blackie [*Pharm. J.*, 1937, **138**, (iv), 84] hydrolysed isatidine, $C_{18}H_{25}O_7N$, with barium hydroxide to isatinecine, $C_8H_{13}O_3N$, and isatinecic acid, $C_{10}H_{16}O_6$, m. p. 143°, whilst with alcoholic potash de Waal (*Onderstepoort J. Vet. Sci. Animal Husb.*, 1939, **12**, 155; 1940, **14**, 445) obtained a "new" isatinecic acid, m. p. 181·5°, having the same formula.

The two alkaloids, retrorsine and isatidine, have been isolated from *S. isatideus* D.C. (Manske, *loc. cit.*) and from *S. retrorsus* D.C. (de Waal, 1939, *loc. cit.*). Barger *et al.* (*loc. cit.*) found only retrorsine in the latter, and de Waal (1939, *loc. cit.*) states that isatidine is always accompanied by retrorsine. In a large number of extractions in these laboratories we have found varying quantities of the two alkaloids from the same sample of *S. isatideus* from which yields as high as 3% of isatidine were obtained when extraction was effected in glass vessels, whilst the quantity of isatidine decreased and that of retrorsine increased to about 1% when extractions were carried out in tinned copper vessels.

Since isatinecine has recently been shown by Leisegang and Warren (Part II) to be retronecine *N*-oxide, it seemed likely that the two alkaloids themselves were closely related. Oxidation and reduction experiments, similar to those previously effected with the "necine" bases, were carried out, and it was found that isatidine was quantitatively reduced by zinc and dilute sulphuric acid to retrorsine which in turn was readily oxidised to isatidine by hydrogen peroxide. It seemed possible that the acid portions were also involved in the oxidation, because de Waal (1940, *loc. cit.*) reports isatinecic acid as a per-acid. On the other hand, the chemical characteristics of the two acids as reported in the literature are different. Barger *et al.* (*loc. cit.*) state that retronecic acid is a dihydroxy-dicarboxylic acid containing two methyl groups, and, since they recovered it unchanged from the hydrogenolysis of retrorsine, Barger and Blackie (*J.*, 1937, 584) assumed it was saturated and must therefore be a cyclic compound. Isatinecic acid, however, is unsaturated and contains one or two double bonds (de Waal, *loc. cit.*).

Hydrolysis of retrorsine by sodium hydroxide under the conditions described by Barger and co-workers (1935, *loc. cit.*) gave isatinecic acid, and not retronecic acid as recorded by these authors. When the same method was repeated with alcohol as the solvent, retronecic acid was found with a melting point and rotation identical with those recorded by de Waal (*loc. cit.*) for his "new" isatinecic acid, obtained by hydrolysis of isatidine with alcoholic potash. Retronecic acid and the "new" acid gave no melting point depression on admixture. Furthermore the brucine salts of the two acids were identical, sintering at 142° and melting at 148°, and differed from the *brucine* salt, $C_{33}H_{42}O_{10}N_2,1\frac{1}{2}H_2O$, m. p. 160—161°, of isatinecic acid.

Isatidine on hydrolysis with aqueous barium or sodium hydroxide gave an impure acid, m. p. 143°, from which was obtained isatinecic acid, m. p. 148°, and a lactone, m. p. *ca.* 186°. The same lactone was obtained by boiling isatinecic acid with alcoholic potash and acidifying to Congo-red, by heating retronecic acid (Barger *et al.*, *loc. cit.*) or isatinecic acid with anhydrous oxalic acid, or by evaporating retronecic acid with concentrated hydrochloric acid. We could not isolate isatinecic acid with a measurable rotation or as its lactone, m. p. 197—198° (de Waal, 1940, *loc. cit.*). In our experiment lactonisation of isatinecic acid gave retronecic acid lactone.

The results are summarised in the table in which are also set out the properties previously recorded.

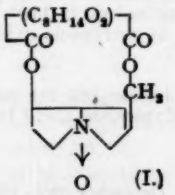
	M. p.	$[\alpha]_D$.	Equiv. wt.
Retronecic acid, $C_{10}H_{16}O_6$, equiv. wt. 116.			
Barger (1935), ex retrorsine	177°	−11·4°	117
de Waal (1940), " new " isatinecic acid	181·5	+56, 0	117·9
Hydrolysis of isatidine by alc. KOH or NaOH	178—180 (*a*)	+28	—
Hydrolysis of retrorsine by alc. KOH	180—181·5 (*b*)	+58	122·7
Isatinecic acid, $C_{10}H_{16}O_6$, equiv. wt. 116.			
de Waal (1940)	148·5	0, +86	117·4
Hydrolysis of isatidine with $Ba(OH)_2$	148·5	0	116·7
Hydrolysis of retrorsine with aq. NaOH	148	0	116
Retronecic acid lactone, $C_{10}H_{14}O_5$, equiv. wt. 214.			
Manske (1931)	186	—	—
Barger (1935)	181—183	—	217
Retronecic acid, evap. with HCl	184—185 (*x*)	*ca.* +66	215
Isatinecic acid lactone, $C_{10}H_{14}O_5$, equiv. wt. 214.			
de Waal (1940)	197—198	+108	217·4
Isatinecic acid with anhyd. oxalic acid	185—186 (*y*)	—	215·6
Isatinecic acid with aq. KOH at 100°	185—186	—	—

Mixed melting point (*a*) and (*b*), 180—181°.
Mixed melting point (*x*) and (*y*), 185—186°.

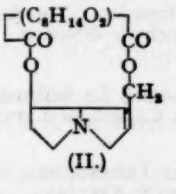
In short, hydrolysis of either retrorsine or isatidine with aqueous barium or sodium hydroxide gave isatinecic acid, whilst with alcoholic sodium or potassium hydroxide or concentrated potassium hydroxide retronecic acid was obtained. A partial interconversion of isatinecic or retronecic acid into retronecic acid lactone was obtained when concentrated mineral acids were used in working up the hydrolysis solutions. A satisfactory procedure for obtaining isatinecic acid was to hydrolyse the alkaloid with barium hydroxide and precipitate the excess of alkali as carbonate. The solution was then evaporated and the basic " necine " extracted to leave pure hydrated *barium isatinecate*, $C_{10}H_{16}O_6Ba,2H_2O$, which readily lost its water of crystallisation at 100°, and from which isatinecic acid was liberated by addition of the exact quantity of dilute sulphuric acid.

A study of the catalytic hydrogenation of both acids showed that they contained one ethylenic linkage. The oily reduction products failed to crystallise and the bis-*p*-bromophenacyl esters could not be induced to solidify, whilst the dibenziminazole (cf. Link, *J. Biol. Chem.*, 1942, **143**, 551) failed to melt below 300°. With *p*-phenylphenacyl bromide the reduction products gave *bis*-p-*phenylphenacyl dihydroisatinecate*, m. p. 117—118°, and *dihydroretronecate*, $C_{28}H_{36}O_8$, m. p. 118—120°, which showed no depression on admixture.

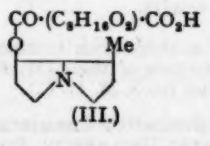
Light-extinction curves for isatinecic acid ($\lambda_{max.}$ at 218 mμ., $\varepsilon_{max.}$ 4720) and retronecic acid ($\lambda_{max.}$ at 218 mμ., $\varepsilon_{max.}$ 9400) reveal these two acids as αβ-unsaturated acids (cf. Andrews, Cristol, Lindenbaum, and Young, *J. Amer. Chem. Soc.*, 1945, **67**, 716).



(I.)



(II.)



(III.)

Ozonolysis of both acids gave acetaldehyde, so that the ethylenic linkages are present as ethylidene groups. It follows, therefore, that isatinecic and retronecic acids are geometrical isomers. Finally, since isatinecic acid has a lower melting point and greater solubility in water and is converted into retronecic acid monolactone on heating with alkali and acid (cf. Auwers and Wissenbach, *Ber.*, 1923, **56**, 715; Fittig, *Annalen*, 1894, **283**, 107), isatinecic acid and retronecic acid are assigned *cis*- and *trans*-configurations, corresponding to angelic and tiglic acids, respectively. It is the *cis*-form in which the acid is attached in the two alkaloids, and the *trans*-form is obtained by isomerisation.

Retrorsine (II) and isatidine (I) may be considered as the *cis*-retronecic (*i.e.*, isatinecic) esters of retronecine and retronecine *N*-oxide, respectively. This relation between the two alkaloids is exactly similar to that found previously by Richardson and Warren (*J.*, 1943, 452) between two other *Senecio* alkaloids, platyphylline and rosmarinine, which are esters of senecic acid with platynecine and hydroxyplatynecine, respectively.

The structure of isatidine is in agreement with de Waal's observation (1940, *loc. cit.*), which we have confirmed, that catalytic reduction gives octahydroanhydroisatidine which may now be formulated as the dihydro-*cis*-retronecic ester (III) of retronecanol.

Experimental.

Interconversion of Retrorsine and Isatinecine.—(*a*) Retrorsine, m. p. 212—214° (corr.) (1 g., 1 mol.), in hot alcohol (10 ml.) was treated with 30% hydrogen peroxide (0·31 ml., 1 mol.), and the mixture maintained at 60° for 6 hours. The solvent was removed under reduced pressure, and the oily residue dissolved in water (20 ml.) and extracted with chloroform to remove unchanged retrorsine. Evaporation of the aqueous solution gave isatidine which, crystallised from ethanol, had m. p. 140·5—141·5°, undepressed on admixture with authentic specimen.

(*b*) Isatidine (5 g., 1 mol.) in 2N-sulphuric acid (50 ml., 7 equivs.) and a few drops of copper sulphate solution was allowed to react with zinc dust for 2 hours at room temperature. The filtered solution was made strongly alkaline with ammonia; the chloroform extract gave an oil which crystallised from chloroform to give retrorsine, m. p. 212—214° (corr.) (darkens at 200°), undepressed with authentic specimen, $[\alpha]_D^{18°}$ −17·6° (*c*, 2·1 in ethanol). Barger *et al.* (*loc. cit.*) give $[\alpha]_D^{18°}$ −17·6°.

Isatinecic Acid.—Isatidine (1 mol.), barium hydroxide (1 mol.), and water (120 mols.) were heated under reflux for 40 minutes, after which carbon dioxide was passed into the hot solution, the barium carbonate was filtered off, and the filtrate and washings were evaporated to dryness in a vacuum. The isatinecine was extracted by hot ethanol to leave pure *barium isatinecate* [Found (after air-drying): Ba, 33·94; (after drying at 100°) Ba, 36·18. $C_{10}H_{14}O_6Ba,2H_2O$ and $C_{10}H_{14}O_6Ba$ require Ba, 34·05 and 37·38%, respectively]. The air-dried salt was treated with the theoretical quantity of dilute sulphuric acid, the barium sulphate filtered off, and the filtrate evaporated in a vacuum, to leave a solid, m. p. 138—139°, raised to 143° after three crystallisations from ethyl acetate. The acid was lixiviated with ethyl acetate to leave a small residue of lactone, m. p. *ca.* 188° (Found: Equiv. Wt., 210). The ethyl acetate gave pure isatinecic acid, m. p. 148° (Found: Equiv. Wt., 116·7). The *brucine* salt formed short needles, m. p. 160—161°, from absolute ethanol (Found: C, 60·60; H, 6·95. $C_{33}H_{42}O_{10}N_2,1\frac{1}{2}H_2O$ requires C, 60·61; H, 6·94%).

Retronecic Acid Lactone from Isatinecic Acid.—Isatinecic acid (3 g.) and potassium hydroxide (1·86 g.) in ethanol (37 ml.) were boiled under reflux for 15 minutes. The potassium salt, which filled the whole liquid with a mass of crystals, was filtered off, washed with absolute alcohol, dissolved in a little water, and acidified to Congo-red. The solution was evaporated on a water-bath, and the residue extracted with ethyl acetate, from which retronecic acid lactone, m. p. 185—186°, crystallised. Repetition with concentrated aqueous potassium hydroxide gave similar results.

Dihydroisatinecic Acid.—Isatinecic acid (1·00 g.) in water (150 ml.) was hydrogenated with Adams's catalyst (0·2 g.), reduced immediately before this hydrogenation in the presence of isatinecic acid; absorption was complete in 200 minutes (observed: 92·7 ml. at S.T.P. Calc. for $C_{10}H_{16}O_6$, 1 mol. = 96·5 ml.). Evaporation of the solvent gave an oily acid, the *bis*-p-*phenylphenacyl* ester of which crystallised from benzene in nodules, m. p. 117—118° (Found: C, 72·80; H, 6·28. $C_{38}H_{36}O_8$ requires C, 73·28; H, 6·16%).

Dihydroretronecic Acid.—Retronecic acid (0·891 g.) was reduced as above at the same rate (observed: 92·7 ml. at S.T.P. Calc.: 86·0) to give an oily acid, the bis-*p*-phenylphenacyl ester of which crystallised from benzene in nodules, m. p. 118—120°, undepressed on admixture with the dihydroisatinecate (Found: C, 73·07; H, 6·10%).

Ozonolysis of Isatinecic and Retronecic Acid.—(*a*) Isatinecic acid (1 g.) in ethyl acetate was ozonised at 0°. The solvent was removed in a vacuum, the ozonide warmed with water, carbon dioxide passed through the solution and then into aqueous dimedon. The flocculent precipitate had m. p. 140°, which was undepressed on admixture with acetaldehyde-dimedon. (*b*) Ozonisation of retronecic acid gave similar results.

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365. *The* Senecio *Alkaloids. Part IV. The Structure of Retronecic and Isatinecic Acids.*

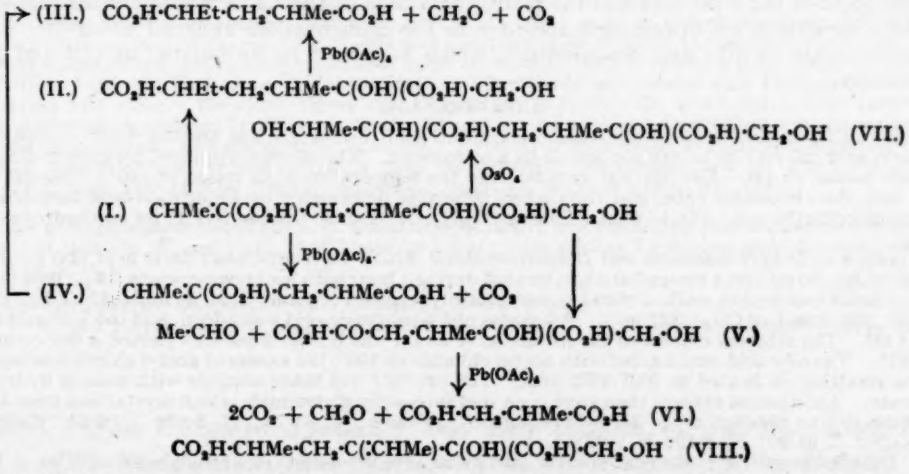
By Stuart M. H. Christie, Meyer Kropman, Lawrence Novellie, and Frank L. Warren.

Isatinecic and retronecic acids are cis- and trans-1 : 2-*dihydroxy*-3-*methylhept*-5-*ene*-2 : 5-*dicarboxylic acid*, (I*b*) and (I*a*), respectively.

The glycol moiety is established by the rapid absorption of two equivalents of oxygen and the formation of formaldehyde with periodic acid and with lead tetra-acetate. The slower consumption of a third equivalent of oxygen with these reagents indicated an α-hydroxy-acid grouping, which was established by the quantitative production of carbon monoxide on treatment with concentrated sulphuric acid, and of carbon dioxide on treatment with lead tetra-acetate.

The two acids give, with lead tetra-acetate in aqueous solution, cis- and trans-α-*methyl*-γ-*ethylideneglutaric acid*, both of which yield the trans-*imide*, whilst the *trans*-acid is hydrogenated to α-methyl-γ-ethylglutaric acid, which in turn is obtained directly by treatment of both dihydroisatinecic and dihydroretronecic (II) acid with lead tetra-acetate. Ozonolysis of retronecic and isatinecic acids, followed by treatment with lead tetra-acetate, gives methylsuccinic acid.

Preliminary experiments with isatinecic acid showed that it contained a glycol grouping because it was readily oxidised with both lead tetra-acetate and periodic acid. With either of these reagents two equivalents of oxygen were rapidly taken up, after which a slower oxidation continued until a third equivalent had been used. The primary nature of one of the hydroxyl groups was revealed by Criegee's glycol test (*Ber.*, 1931, **64**, 260), and by oxidation with two equivalents of lead tetra-acetate to give 0·75 mole of formaldehyde, identified as its dimedon compound. The consumption of the third equivalent of oxygen indicated that the second hydroxyl group was in an α-position to a carboxyl group. That isatinecic acid was an α-hydroxy-acid was confirmed by the formation of a yellow colour with dilute ferric chloride solution (cf. Mitchell, Weinstock, Snell, Stanbery, and Williams, *J. Amer. Chem. Soc.*, 1940, **62**, 1776; Berg,



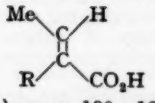
Bull. Soc. chim., 1894, [iii], **11**, 883) and by the production of 0·75 mole of carbon monoxide on treatment with concentrated sulphuric acid (cf. Mitchell *et al.*, *loc. cit.*; Bistrzycki and Siemiradzki, *Ber.*, 1906, **38**, 52).

Use of exactly two equivalents of lead tetra-acetate in glacial acetic acid gave only an oily product, so an attempt was made to effect oxidative degradation with the same reagent in aqueous solution whereby the intermediate keto-acid would also be oxidised (cf. Baer, *J. Amer. Chem. Soc.*, 1940, **62**, 1597). Dihydroisatinecic acid was treated in the same manner, whereby, after an initial induction period probably associated with the primary fission of the glycol, a steady evolution of one mole of carbon dioxide was observed.

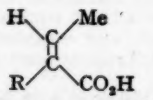
The oily reaction product slowly deposited a few crystals of an acid, m. p. 67°, and the oil gave an imide, $C_8H_{13}O_2N$, m. p. 113—114°, corresponding to α-methyl-γ-ethylglutaric acid (III) and its imide which Rydon (*J.*, 1936, 1444) reports as melting at 63° and 116°, respectively. Repetition of this oxidation with dihydroretronecic acid gave the same imide. In the absence

of an authentic specimen further degradation was necessary. Retronecic and isatinecic acid were accordingly first ozonised and then oxidised with lead tetra-acetate. In conformity with structure (I) for these two acids and with the intermediate formation of the acid (V) on ozonisation, the treatment with lead tetra-acetate gave two moles of carbon dioxide and methylsuccinic acid (VI), characterised further as its acid strychnine salt.

Structure (VIII) would also be capable of giving degradation products (III) and (VI); but this formula was excluded in that oxidation of isatinecic acid with osmium tetraoxide gave a compound with equivalent weight corresponding to dihydroxydihydroisatinecic acid, $C_{10}H_{18}O_8$,



(I*a*.), m. p. 180—181·5°
(IV*a*.), m. p. 151°



(I*b*.), m. p. 148·5°
(IV*b*.), m. p. 95°

(I*a*.) and (I*b*.) : R = $-CH_2\cdot CHMe\cdot C(OH)(CO_2H)\cdot CH_2\cdot OH$
(IV*a*.) and (IV*b*.) : R = $-CH_2\cdot CHMe\cdot CO_2H$

m. p. 245°. A compound with structure (VIII) would yield a γ-hydroxy-acid which would be expected to give a lactone. Furthermore, formula (I) is in agreement with spectroscopic data for both retronecic and isatinecic acid (Christie, Kropman, Leisegang, and Warren, preceding paper).

That the two acids were geometrical isomers was shown by oxidation with aqueous lead tetra-acetate to remove the glycol grouping and preserve the ethylenic centres. Retronecic acid yielded trans-*α-methyl-γ-ethylideneglutaric acid*, $C_8H_{12}O_4$ (IV) and (IV*a*), m. p. 151°, which gave the trans-*imide*, $C_8H_{11}O_2N$, m. p. 90°, and which on catalytic hydrogenation gave α-methyl-γ-ethylglutaric acid (III) (identified as the imide, m. p. 120—121°). Isatinecic acid, on the other hand, gave cis-*α-methyl-γ-ethylideneglutaric acid* (IV) and (IV*b*), m. p. 95°, which yielded an imide, m. p. 90°, identical with that from the *trans*-acid (IV*a*). Hydrolysis of the imide gave the *trans*-acid (IV*a*.). These geometrical configurations are assigned from consideration of the higher melting point of the *trans*-acid and the ready conversion of the *cis*-form into the *trans*-imide.

These structures are in complete accord with the configurations assigned to isatinecic and retronecic acids as *cis*- and *trans*-isomers, which may now be formulated as (I*b*) and (I*a*), respectively.

Experimental.

Action of Concentrated Sulphuric Acid.—Isatinecic acid (0·2153 g.) was treated with concentrated sulphuric acid (25 ml.) in a flask connected to a nitrometer. The air was displaced by carbon dioxide, the flask heated at 140—150° for 100 minutes, and the temperature then raised to 180°. The gas was swept into the nitrometer tube, and the carbon monoxide determined by absorption with ammoniacal cuprous chloride (Found : CO, 14·6 ml. Calc. for $C_{10}H_{16}O_6$: CO, 20·8 ml. at N.T.P. for one hydroxy-acid group).

Oxidation of Dihydroisatinecic and Dihydroretronecic Acid.—(*a*) Dihydroisatinecic acid (3·5 g., 0·015 mol.) in water (60 ml.) on a steam-bath was treated during 1 hour with lead tetra-acetate (14 g., 0·03 mol.). After an induction period, carbon dioxide was steadily evolved (Found : CO_2, 304 ml. at N.T.P. Calc. for $C_{10}H_{18}O_6$, 1 mol. of CO_2 : 337 ml.). An excess of 5N-sulphuric acid was added, and the lead sulphate filtered off. The ethereal extract of the filtrate gave an oil which after 2 months yielded a few crystals, m. p. 67°. The oily acid was treated with acetyl chloride at 100°, the excess of acetyl chloride removed, and the resulting oil heated to 200° with urea. The product was made alkaline with sodium hydrogen carbonate. An ethereal extract then gave *cis-α*-methyl-γ-ethylglutarimide which crystallised from light petroleum in fine needles, m. p. 113—114° (uncorr.) (Found : C, 61·75; H, 8·64; N, 8·83. Calc for $C_8H_{13}O_2N$: C, 61·90; H, 8·45; N, 9·03%).

(*b*) Dihydroretronecic acid under similar conditions gave *cis-α*-methyl-γ-ethylglutarimide, m. p. 114° (uncorr.), undepressed by admixture with the imide obtained from dihydroisatinecic acid. Recrystallisation from light petroleum gave crystals, m. p. 120—121°, hydrolysed by concentrated hydrochloric acid to *cis-α*-methyl-γ-ethylglutaric acid, m. p. 72—73° (equiv. wt., 86·8). Rydon (*J.*, 1936, 1944) gave m. p.s of *cis-α*-methyl-γ-ethylglutaric acid (unanalysed) and of its imide as 63° and 116°, respectively.

Oxidations of Retronecic and Isatinecic Acids.—(i) *With periodic acid.* (*a*) Isatinecic acid (*ca.* 0·1 g.) was treated with 0·5N-periodic acid (2 ml.) and set aside. The solution was neutralised with sodium hydrogen carbonate and then treated with 0·1N-sodium arsenite (25 ml.) and 20% potassium iodide (1 ml.), and the excess of arsenite determined iodometrically.

(*b*) The oily dihydroisatinecic acid obtained by catalytic reduction of isatinecic acid was dissolved in water, the concentration was determined by titration, and aliquot portions of 0·1 g. were treated as above, with the following results.

Time (hours)	0·25	0·5	1	2	3	4	16½
				Equivalents of oxygen.			
Isatinecic acid	2·01	2·4	—	—	2·9	—	3·6
Dihydroisatinecic acid	1·6	2·0	2·1	2·2	2·4	2·7	2·9

(*c*) Isatinecic acid (208 mg., 1 mol.), allowed to react with 0·1N-periodate for 45 minutes under the conditions of Reeves (*J. Amer. Chem. Soc.*, 1941, **63**, 1476), gave formaldehyde-dimedon (197 mg., 0·75 mol.), m. p. 190—192°, undepressed by admixture with an authentic specimen.

(ii) *With lead tetra-acetate.* (*a*) Isatinecic acid (*ca.* 0·1 g.) was treated with 0·1N-lead tetra-acetate in glacial acetic acid and set aside. The excess of tetra-acetate was later determined iodometrically. Separate determinations showed that after 0·5, 1, 2, 4, and 9 hours 2·1, 2·3, 2·7, 3, and 3·1 equivalents, respectively, of oxygen were absorbed.

(*b*) Retronecic acid (3·4 g.) was treated with lead tetra-acetate as described for the dihydro-acid (Found : CO_2, 309 ml. Calc. for $C_{10}H_{16}O_6$: CO_2, 328 ml. at N.T.P.). The steam-distillate gave with dimedon the formaldehyde compound, m. p. 186° (uncorr.). The solid from the ethereal extract was crystallised from water to give trans-*α-methyl-γ-ethylideneglutaric acid* as needles, m. p. 151° (uncorr.) (Found : C, 55·86; H, 7·10; equiv. wt., 86·2. $C_8H_{12}O_4$ requires C, 55·82; H, 7·03%; equiv. wt., 86·0). The *imide*, prepared as above and obtained as a solid on the addition of the sodium hydrogen carbonate, was crystallised three times from light petroleum, to give needles, m. p. 90° (single crystal) (Found : C, 62·99; H, 6·80; N, 9·35. $C_8H_{11}O_2N$ requires C, 62·72; H, 7·24; N, 9·14%).

Hydrogenation of the acid in the presence of Adams's catalyst gave an oily acid yielding an imide, m. p. 120—121°, undepressed on admixture with *cis*-α-methyl-γ-ethylglutarimide obtained above.

(*c*) Isatinecic acid (3·5 g.) was treated similarly with lead tetra-acetate (Found : CO_2, 334 ml. Calc. for $C_{10}H_{16}O_6$: 336 ml. at N.T.P.). The oily product from the ethereal extract partly solidified on treatment with concentrated hydrochloric acid. The solid, removed from the oil on a porous plate, crystallised from chloroform–light petroleum to give cis-*α-methyl-γ-ethylideneglutaric acid* as colourless microscopic crystals, m. p. 95° (uncorr.) (Found: C, 55·58; H, 7·17; equiv. wt., 89·4. $C_8H_{12}O_4$ requires C, 55·78; H, 7·03%; equiv. wt., 86). The imide, prepared as above, crystallised from light petroleum in needles, m. p. 90°, undepressed on admixture with the imide from the *trans*-acid. Hydrolysis of this imide with concentrated hydrochloric acid gave the *trans*-acid, m. p. 150°, undepressed on admixture with an authentic specimen.

(iii) *With ozone and lead tetra-acetate.* (*a*) Isatinecic acid (3 g., 0·013 mol.) was ozonised as above, and the product decomposed by water and treated at 100° with lead tetra-acetate (18 g., 0·04 mol.) as above (CO_2 evolved : 502 ml. at N.T.P. Calc. for $C_{10}H_{16}O_6$, 2 mols. of CO_2, 578 ml.). Treatment as for the dihydroisatinecic acid gave a solid which, crystallised from benzene, yielded methylsuccinic acid, m. p. 98°, undepressed by an authentic specimen, m. p. 102° (Found : C, 45·55; H, 6·20; equiv. wt., 66·5. Calc. for $C_5H_8O_4$: C, 45·42; H, 6·10%; equiv. wt., 66·0). Hydrogen strychnine methylsuccinate had m. p. 185° (Ladenburg, *Ber.*, 1895, **28**, 1170, gives m. p. 186°).

(*b*) Rectronecic acid, oxidised similarly, gave methylsuccinic acid, m. p. 109—110° (equiv. wt., 68·17) (hydrogen strychnine salt, m. p. 185°).

(iv) *With osmium tetraoxide.* Isatinecic acid (1 g., 0·004 mol.) in anhydrous ether (250 ml.) was treated with osmium tetraoxide (1 g., 0·004 mol.) and set aside at room temperature for 5 days. The solvent was removed, and the residue heated under reflux with sodium sulphite (10 g.) in water (100 ml.) and ethanol (25 ml.) for 3 hours and then filtered. The filtrate was treated with hydrochloric acid and extracted with ether. The extract gave a small quantity of black solid, which was heated under reflux with potassium hydroxide (1 g.) in methanol (20 ml.) for 3 hours and decolorised with charcoal. The solvent was removed, and the solution acidified. Extraction with ether, evaporation, treatment of the residue with ethyl acetate and filtration gave *dihydroxydihydroisatinecic acid* as colourless crystals (20 mg.), m. p. 245° (Found : equiv. wt., 134. $C_{10}H_{18}O_8$ requires equiv. wt., 133).

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366. *The Enzymic Synthesis and Degradation of Starch. Part IV. The Purification and Storage of the Q-Enzyme of the Potato.*

By S. A. BARKER, E. J. BOURNE, and STANLEY PEAT.

An improved method is described for the isolation and purification of the Q-enzyme of potatoes. The Q-enzyme prepared by this method effects almost a 90% diminution of the absorption value of amylose with the concomitant liberation of only 2% (as maltose) of reducing end-groups. The preparation is free from α- and β-amylase, maltase, and fatty acids.

The amylose-degrading action of Q-enzyme functions at optima of pH 7·0 and temperature, 21° ± 1°.

Although Q-enzyme is unstable in aqueous solution, it can be stored for long periods without appreciable loss in activity when it is freeze-dried.

IN 1940, Hanes (*Proc. Roy. Soc.*, 1940, *B*, **129**, 174) isolated from potato juice a phosphorylase (P-enzyme), which catalysed the synthesis, from dipotassium glucose-1 phosphate, of a polysaccharide resembling the amylose component of potato starch in its degree of hydrolysis with β-amylase and in its ability to give a blue stain with iodine. An end-group assay, carried out

two years later by Haworth, Heath, and Peat (*J.*, 1942, 55), revealed that this polysaccharide consisted of unbranched chains, averaging 80—90 units in length, of 1 : 4-linked α-glucose members, and thus confirmed that it was indeed an amylose. Since the major component of potato starch is not amylose, but amylopectin, a red-staining polyglucose having a branched structure in which chains of approximately 20 glucose members are united by cross-linkages, it was evident that a second enzyme figured prominently in the synthesis of starch *in vivo*. This supplementary enzyme was isolated from potatoes by Haworth, Peat, and Bourne (*Nature*, 1944, **154**, 236) and was named, provisionally, Q-enzyme. Unlike P-enzyme, it does not use glucose-1 phosphate as a substrate (Bourne and Peat, *J.*, 1945, 877). The synthesis of amylopectin from the Cori ester probably involves catalysis by P-enzyme of the end-wise apposition of glucose residues until the linear chains reach such a length that they serve as a substrate for Q-enzyme, which establishes cross-links between the chains to give a branched structure. In this respect Q-enzyme is similar to an enzyme found in liver and heart (Cori, Swanson, and Cori, *Federation Proc.*, 1945, **4**, 234). Q-Enzyme possesses a dual function since it converts amylose itself into amylopectin by a hydrolytic, as opposed to a phosphorolytic, process (Bourne and Peat, *J.*, 1945, 877; Bourne, Macey, and Peat, *J.*, 1945, 882).

Q-Enzyme has hitherto been isolated by treating potato juice with kaolin under the conditions described by Waldschmidt-Leitz and Mayer (*Z. physiol. Chem.*, 1935, **236**, 168) for the adsorption of amylases, and thereafter precipitating the Q-enzyme from the supernatant liquid with neutral ammonium sulphate (16 g./100 c.c.), leaving the bulk of the P-enzyme in solution. The enzyme was further purified by re-fractionation with ammonium sulphate (Bourne and Peat, *J.*, 1945, 877). Although this method yields a Q-enzyme reasonably free from α- and β-amylases when applied to freshly-harvested potatoes, it gives enzyme preparations progressively richer in amylases from potatoes which have been stored. In addition, the efficiency of the adsorption process varies with different batches of kaolin.

We have now developed an alternative method of isolation by which Q-enzyme preparations substantially free from the other enzymes of this group are obtained as free-flowing powders. A preliminary account of this method was given by Peat, Bourne, and Barker in 1948 (*Nature*, **161**, 127). The method gives reproducible results with potatoes during their " resting period," but not, as yet, with potatoes in which sprouting has commenced. Since however it is now possible to store Q-enzyme for prolonged periods, we have adopted the policy of preparing a stock of the enzyme from young potatoes for use at less favourable seasons.

The new method, developed from one applied to yeast for a different purpose by Minagawa (*J. Agric. Chem. Soc. Japan*, 1932, **8**, 1068), involves (i) precipitation from potato juice of Q-enzyme and other proteins by the addition of lead acetate at pH 7·25, (ii) elution of the lead–protein complex with sodium hydrogen carbonate solution, through which a stream of carbon dioxide is passed, and (iii) precipitation of the enzyme (fraction Q1) from the supernatant liquid with neutral ammonium sulphate (19 g./100 c.c.). A small amount of enzyme (fraction Q2) remains in solution, and is precipitated, together with P-enzyme, when the concentration of ammonium sulphate is increased to 35 g./100 c.c. Fraction Q1 can be further purified by reprecipitation with neutral ammonium sulphate (19 g./100 c.c.), giving fraction Q3. Each stage of the method has been carefully investigated to ensure that it is carried out under optimum conditions.

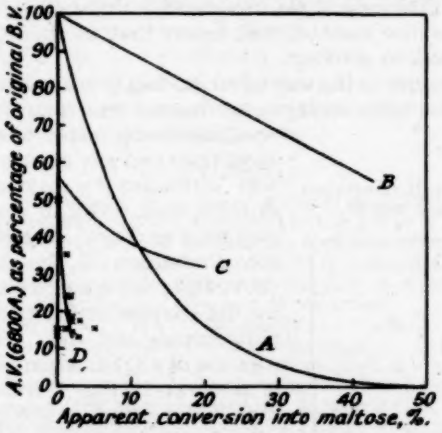
Fraction Q1 shows only a slight copper-reducing value and is free from maltase inasmuch as no increase in reducing power follows when it is incubated with maltose in acetate buffer at pH 7. Fraction Q3, which is also free from maltase, is non-reducing. None of the many samples of fractions Q1 and Q3 prepared by us has been contaminated with the fatty acids which are normally present in potato juice. Fatty acids form insoluble complexes with amylose (Schoch and Williams, *J. Amer. Chem. Soc.*, 1944, **66**, 1232), and their presence in an enzyme preparation precludes its use in quantitative studies on starches or on starch fractions containing amylose. These acids were probably removed as lead salts during the isolation of the enzymes.

Bourne, Macey, and Peat (*J.*, 1945, 882) distinguished Q-enzyme from the normal amylases by plotting " absorption value (A.V.) (6800 A.) " against " apparent percentage conversion into maltose " during the incubation of the enzymes with amylose. Each enzyme gave a characteristic curve, which was independent of enzyme concentration. A typical graph for Q-enzyme (fraction Q1), prepared by the new method, is shown in Fig. 1; this graph (*D*) is plotted from results obtained with about ten different samples of fraction Q1. It demonstrates unequivocally that this Q-enzyme preparation is different from either α- or β-amylase (curves *A* and *B*), and is moreover appreciably purer than the Q-enzyme previously isolated by the kaolin method

(curve *C*). Fraction Q1 effects an 87% reduction in A.V. (6800 A.) at a stage when the "apparent percentage conversion into maltose" is only 2%. If the Q1 preparation is contaminated by either α- or β-amylase, the concentrations of these impurities must be extremely small, too small, in fact, to be detected by the usual methods of estimation. The efficiency of the removal of lead ion during the treatments with sodium hydrogen carbonate and ammonium

FIG. 1.

The hydrolysis of amylose by Q-enzyme and amylases.



A.—aβ-*Amylase from saliva.*
B.—β-*Amylase from soya bean.*
C.—*Q-Enzyme from young potatoes* (*kaolin method*).
D.—*Enzyme fraction Q1* (*lead acetate method*).
Curves A, B, and C were given by Bourne, Macey, and Peat (J., 1945, 882).

sulphate is demonstrated by the fact that the introduction of only 6×10^{-4}M-lead acetate decreases the activity of a Q1 preparation by about 80%.

The optimum conditions of temperature and pH for the amylolytic activity of Q-enzyme have been ascertained as follows. Aliquot portions of a solution of fraction Q1 were incubated with amylose in the presence of veronal buffers, which differed in their pH values only by virtue of

FIG. 2.

The effect of pH on the hydrolysis of amylose (*B.V.*, 1·04) *by Q-enzyme at* 20·5°.

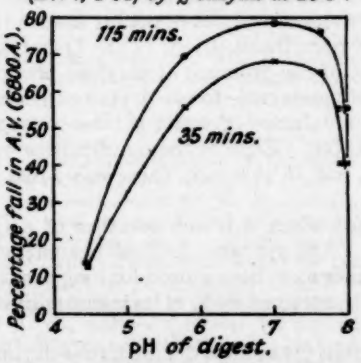
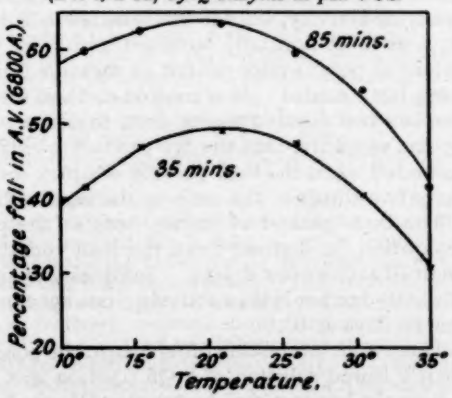


FIG. 3.

The effect of temperature on the hydrolysis of amylose (*B.V.*, 1·04) *by Q-enzyme at pH* 7·04.



the amount of sodium hydroxide added (Fig. 2). The optimum pH for the enzyme is 7·0; the activity declines sharply above pH 7·5 and below pH 6·5. The optimum pH for this preparation of Q-enzyme is higher than that for either β-amylase (*ca.* 5·0) or P-enzyme (*ca.* 6·0), but is approximately the same as that for α-amylase (*ca.* 7·0). In a second series of digests, fraction Q1 was incubated with amylose (pH 7·04) at temperatures ranging from 11° to 35°

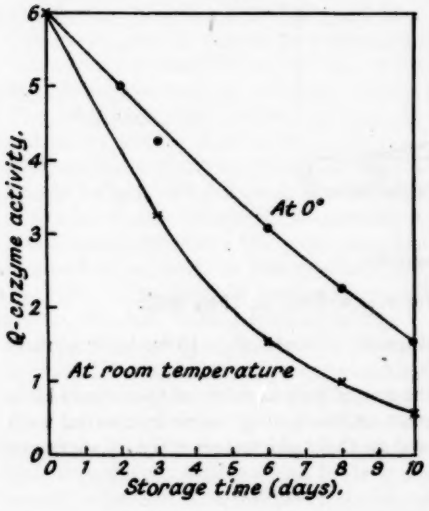
(Fig. 3). The optimum temperature (21° ± 1°) was unusually low in comparison with the optima of other enzymes concerned in starch metabolism. The rate of hydrolysis of amylose by Q-enzyme falls rapidly below 17° and above 26°. At 35°, the usual temperature for incubations of this kind, the enzyme exhibits less than 50% of its maximum activity.

One of the major difficulties encountered in the earlier work on Q-enzyme was the impossibility of keeping a stock of the enzyme. For each experiment, however small, it was necessary to prepare fresh enzyme and to check its purity immediately before use. Furthermore, the work was confined to a short period of the year, following the harvest, when the amylase content of potatoes was small. For this reason, we investigated the conditions of storage of Q-enzyme specimens prepared by the new method, and report that fraction Q1 may be stored for long periods with only a slight loss in activity.

There are obvious difficulties in the way of estimating Q-enzyme activity in terms of absolute units, and therefore to place these storage experiments on a quantitative basis, the Q-enzyme specimen being tested was stored under a variety of conditions and any change of activity which occurred was estimated by comparison with the effect of dilution with water of a solution of that particular sample of enzyme. As criterion of activity was taken the diminution of the A.V. (6800 A.) of amylose (B.V. 1·04; see Experimental) produced in unit time by the enzyme acting under optimum conditions of temperature and pH. The effect of storage of a solution of a Q1 fraction at room temperature and at 0° is shown in Fig. 4, from which it is seen that at room temperature only 50% of the activity remained after 3·4 days, whereas at 0° 6·2 days were required for the same loss of activity. A second experiment showed that the half life of the enzyme was about 15 and 4 minutes at 45·5° and 55·5°, respectively.

FIG. 4.

The stability of enzyme fraction Q1 in aqueous solution at room temperature and 0°.



It was clearly not feasible to store a Q1-fraction in the dissolved state, and attention was directed to the stability of the dry enzyme. The use of alcohol as a precipitant and drying agent was precluded by the fact that Q-enzyme is extensively inactivated by alcoholic precipitation, even at 0° (Bourne, Macey, and Peat, *J.*, 1945, 882). It was decided, therefore, to freeze-dry Q-enzyme at various stages during its isolation from potato juice by the lead acetate method. Potato juice, itself, was dried in the frozen state on several occasions with little, or no, loss of Q-enzyme activity, since it was possible to isolate from the products samples of the Q1 fraction as active as those normally obtained from juice which had not been freeze-dried. (The Q-enzyme content of potato juice cannot be measured directly because of the presence of amylose-precipitating fatty acids.) As a routine method for the storage of Q-enzyme, freeze-drying of potato juice has two disadvantages, first, that the removal of large volumes of water is time-consuming, and secondly, that the dry product is extremely hygroscopic. Each of these difficulties was eliminated when the lead–protein complex was freeze-dried, but, in this case, there was a loss of nearly two-thirds of the activity during the drying process.

The best method of storage was as the powder obtained when a frozen solution of a Q1 preparation, as distinct from the lead complex, was dried. On average, 70% of the enzyme remained active after drying. Samples prepared in this manner have been stored for long periods with little further loss in activity; one specimen, for example, retained 84% of its initial activity after 50 days at 0°.

There is an interesting difference in the behaviour of fractions Q1 and Q3 during freeze-drying. When a frozen solution of a Q3 fraction was dried, the activity decreased by more than 90%, whereas the loss incurred by fraction Q1 was less than 30%. It is probable that the inactivation was caused by an increase in acidity, resulting from the removal of ammonia from ammonium sulphate present in the enzyme solutions. In the case of a Q1 preparation, non-enzymic proteins and traces of sodium hydrogen carbonate serve as buffers and prevent a marked fall in pH, whereas the purer Q3 fraction is not adequately buffered in this way. Thus, when a small volume of boiled potato juice was added to the Q3 fraction before freeze-drying, the loss of activity was not

more than 20%. It may well be that there is a similar explanation of the destruction of P-enzyme during freeze-drying (*cf.* Weibull and Tiselius, *Arkiv Kemi, Min., Geol.*, 1945, **19**, *A*, No. 19). We intend to study the freeze-drying of both purified P-enzyme and Q-enzyme in the presence of strong buffers in order to elucidate these points.

The freeze-drying of Q1 fractions effects, unexpectedly, a further purification. Whereas a Q1 preparation normally contains about 10% of the P-enzyme initially present in the juice, the freeze-dried product contains only about 4%. This P-enzyme content is further reduced to below 1% by reprecipitation with neutral ammonium sulphate at 19 g./100 c.c. There is thus strong support for the belief, expressed by Bourne and Peat (*J.*, 1945, 877), that Q-enzyme, when free from P-Enzyme, has no action on glucose-1 phosphate.

As a result of these studies, we have prepared a stock of very active Q-enzyme (at the Q1 stage of purification) for further investigations concerning the synthesis of amylopectin and the conversion of amylose into amylopectin. Some of the results of these investigations are reported in the communication (Part V) which follows.

Experimental.

Analytical Methods.—(a) *Measurement of the iodine stains of polysaccharides.* The two expressions, Absorption Value (A.V.) and Blue Value (B.V.), employed in this paper to describe the intensities of the iodine stains of polysaccharides, were defined by Bourne, Haworth, Macey, and Peat (*J.*, 1948, 924). Whereas the B.V. is determined under standard conditions of concentration and at λ 6800 A. and is therefore characteristic of the polysaccharide in question, the A.V. is simply a convenient term used for the comparison of intensities made under any given set of conditions.

(b) *Determination of reducing sugar.* The copper reagent of Shaffer and Hartmann (*J. Biol. Chem.*, 1921, **45**, 377) was used for the determination of reducing sugars. For the determination of small quantities of sugar ($< 0{\cdot}2$ mg. of glucose and $< 0{\cdot}4$ mg. of maltose), a known weight of the appropriate sugar was introduced and the amount originally present was calculated by difference.

(c) *Determination of inorganic- and ester-phosphorus.* A colorimetric method (Allen, *Biochem. J.*, 1940, **34**, 858) was used for the determination of inorganic phosphorus (free P). The total phosphorus (free P + ester-P) was determined, after acid hydrolysis, by the same method and the ester-P was calculated by difference.

(d) *Determination of phosphorylase.* Phosphorylase activity was measured by the method of Green and Stumpf (*J. Biol. Chem.*, 1942, **142**, 355) and is expressed in the units defined by them.

Preparation of Starch Fractions.—The amylose and amylopectin used in this work were derived from potato starch by selective precipitation of the former with thymol, according to the standard procedure of Bourne, Donnison, Haworth, and Peat (*J.*, 1948, 1687).

Standard Method for the Isolation of Q-Enzyme.—All operations were performed at room-temperature.

(a) *Extraction of potato juice.* King Edward potatoes (1 kg.) were peeled, thinly sliced, and soaked for 20 minutes in water (1 l.), containing 0·5% of sodium hydrosulphite [dithionite]. The slices were drained, washed, minced, and pressed. The light-yellow juice was clarified by centrifuging and immediately subjected to the following fractionation procedure.

(b) *Preparation of lead acetate solution.* A solution (approx. 1 l.) of lead acetate (190 g.) was adjusted with N-sodium hydroxide to pH 7·25, and set aside for a few days. After removal of the precipitated material, the solution was diluted with water to 3 l.

(c) *Treatment with lead acetate and fractionation with ammonium sulphate.* To each 100 c.c. of juice, 0·02N-sodium hydroxide (40 c.c.) was added, with stirring; the pH of the solution was then 7·2. After the addition of water (30 c.c.), lead acetate solution (30 c.c.) was introduced and the yellow lead–protein precipitate was removed by the centrifuge, the supernatant liquid (pH 6·85) being discarded. The precipitate was stirred with 0·2N-sodium hydrogen carbonate (100 c.c.) for 5 minutes, and a stream of carbon dioxide was then passed through the suspension for 2½ minutes. The insoluble residue was removed by the centrifuge and discarded. To the supernatant liquid (*ca.* 110 c.c.) ammonium sulphate solution (pH 7; 50 g./100 c.c.) was added to give a final ammonium sulphate concentration of 19 g./100 c.c. The precipitate (fraction Q1) was collected and redissolved in water (20 c.c.). In some cases it was re-fractionated by a similar precipitation with ammonium sulphate, the product (fraction Q3) being redissolved in water (20 c.c.).

Standard Digest for the Hydrolysis of Amylose by Q-Enzyme.—Amylose (dry weight, *ca.* 220 mg.; B.V., 1·04) was moistened with ethanol (1 c.c.), and 0·5N-sodium hydroxide (12 c.c.) added. Dissolution of the amylose was completed by heating in a boiling water-bath for 3 minutes. The solution was cooled and diluted with water to 100 c.c. A portion containing 186·6 mg. of amylose was exactly neutralised to phenolphthalein with 0·5N-sulphuric acid and diluted to 100 c.c. This solution, which contained 14 mg. of amylose in 7·5 c.c., was incorporated in a digest, consisting of amylose solution (7·5 c.c.), maltose solution (1·5 c.c., equiv. to 3·0 mg. of maltose), M-acetate buffer (2·5 c.c.; pH 7·04), and enzyme solution (2·5 c.c.), making a total volume of 14 c.c. After a suitable period of incubation at 20·5°, an aliquot portion (4 c.c.) was submitted to the Shaffer–Hartmann determination of reducing sugar. Another portion (1 c.c.) was stained with iodine (2 mg.)–potassium iodide (20 mg.) in a final volume of 100 c.c., the A.V. being measured in the usual manner. A control digest, containing water (7·5 c.c.) instead of the amylose solution, was simultaneously incubated at 20·5°, and the reducing power was measured periodically. The difference between the reducing values of the two digests was a measure of the reducing groups liberated by the action of the enzyme on amylose and is expressed in terms of "apparent maltose".

Development of the Standard Method for the Isolation of Q-Enzyme.—(a) *Optimum conditions for precipitation of the lead complex.* Portions (100 c.c.) of the same sample of potato juice were adjusted to

varying pH values with 0·02N-sodium hydroxide and diluted with water so that, on addition of lead acetate solution (30 c.c., see above) of the same pH, the final volume was 200 c.c. The precipitated lead–protein complex was collected by the centrifuge, the Q-enzyme being subsequently eluted as described above and precipitated once with ammonium sulphate, as in the earlier method, except that the concentration of ammonium sulphate was 16 g./100 c.c. The enzyme was redissolved in water (20 c.c.) and tested for Q-enzyme activity by incubation with amylose.

To the supernatant liquid remaining after the removal of the lead–protein complex, ammonium sulphate solution (pH 7; 50 g./100 c.c.) was added to give a salt concentration of 16 g./100 c.c. The precipitate was stirred with water (20 c.c.) and centrifuged, and the clear solution tested for Q-enzyme activity.

pH of juice and lead acetate.		Enzyme fraction during lead acetate treatment.	Test for Q-enzyme (19 hrs.).	
Before mixing.	After mixing and centrifuging.		Fall (%) in A.V. (6800 A.).	Apparent conversion into maltose (%).
6·15	5·41	Precipitate	82·6	0
		Solution	5·8	1·4
6·76	6·09	Precipitate	86·6	2·4
		Solution	3·9	0
7·54	7·09	Precipitate	87·6	0
		Solution	20·2	1·0
8·49	8·48	Precipitate	76·0	1·0
		Solution	50·0	0

A graph of the above results revealed that the maximum amount of Q-enzyme was precipitated from potato juice by lead acetate when the two solutions had pH 7·25 before mixing.

(b) *Optimum conditions for elution of the lead complex.* Portions (100 c.c.) of the same sample of potato juice were treated with lead acetate by the standard method, and the precipitated lead–protein complexes eluted by stirring for 5 minutes at room temperature with various solutions (100 c.c.). In each case, after centrifuging, ammonium sulphate solution (pH 7·0; 50 g./100 c.c.) was added to the supernatant liquid to give a final concentration of ammonium sulphate of 18·3 g./100 c.c. Each precipitate was collected by centrifuging, stirred with water (20 c.c.), freed from insoluble material, and tested for Q-enzyme activity by incubation with amylose.

Solution used for elution (100 c.c.).	Fall (%) in A.V. (6800 A.) of amylose (30 mins.).
(1) $NaHCO_3$–CO_2 as in standard method	67·8
(2) Retreatment after (1)	26·0
(3) Water	1·0
(4) $NaHCO_3$–CO_2 after elution with water as in (3)	55·8
(5) $NaHCO_3$ as in standard method (no CO_2)	63·3
(6) 0·01N-NaOH	1·9

(c) *Optimum conditions for the precipitation of the Q1-enzyme fraction.* Portions (100 c.c.) of the same sample of potato juice were treated with lead acetate and then with sodium hydrogen carbonate–carbon dioxide, as in the standard method. To the eluate, varying proportions of ammonium sulphate solution (pH 7; 50 g./100 c.c.) were added, such that the final concentrations of ammonium sulphate were those recorded in the following table. Each enzyme precipitate was separated, redissolved in water (20 c.c.), and tested for Q-enzyme activity by incubation with amylose.

Concentration of ammonium sulphate (g./100 c.c.).	Fall (%) in A.V. (6800 A.) of amylose (30 mins.).	Units (Green & Stumpf) of P-enzyme from 100 c.c. of juice.
12·5	11·5	—
14·7	60·6	—
18·3	71·3	—
19·0	72·3	17·1
23·5	66·5	—
30·3	61·5	—
32·3	60·4	—
35·0	—	150

When the above results were plotted, it was clear that the most suitable concentration of ammonium sulphate for the precipitation of the Q1 fraction was 19 g./100 c.c. At this concentration only about 11% of the P-enzyme in the juice was precipitated with Q1.

Inhibition of Q-Enzyme by Lead Ions.—A sample of fraction Q1, prepared from potato juice by the standard method, was dissolved in water (20 c.c.). Portions of this solution were incubated with amylose, as in the standard estimation of Q-enzyme, with two variations: (*a*) the amylose solution was neutralised with acetic acid instead of sulphuric acid, and (*b*) lead acetate was incorporated in the digests in the concentrations shown in the following table.

Molarity of lead acetate in digest.	Fall (%) in A.V. (6800 A.) of amylose (30 mins.).
None	71·9
$1·49 \times 10^{-6}$	70·7
$2·98 \times 10^{-5}$	69·6
$1·98 \times 10^{-4}$	63·1
$5·95 \times 10^{-4}$	53·8

Optimum pH for the Action of the Q1-Enzyme Fraction on Amylose.—A sample of fraction Q1, prepared from potato juice (300 c.c.) by the standard method, was dissolved in water (60 c.c.). Portions (2·5 c.c.) of the solution were incubated with amylose under the conditions prescribed above, except that the acetate buffer was replaced by veronal buffers of different pH values; the latter buffers differed only in the amount of sodium hydroxide added. Since the veronal buffers were dilute, they did not retain their initial pH values when incorporated in the digests and it is, therefore, the pH values of the digests which are recorded in Fig. 2. The freedom, from amylases, of the Q1 fraction used was demonstrated by the fact that, at pH 7·04, which is near the optimum for α-amylase, the " apparent conversion into maltose " was only 0·5% when the fall in A.V. (6800 A.) was 78·5%.

Optimum Temperature for the Action of the Q1-Enzyme Fraction on Amylose.—A sample of fraction Q1, prepared from potato juice (300 c.c.) by the standard method and dissolved in water (60 c.c.), was incubated with amylose, as in the standard digest, except that (*a*) the acetate buffer was replaced by veronal buffer, such that the digests had pH 7·04, and (*b*) the temperature of incubation ranged from 11° to 35°. The results are recorded in Fig. 3. The Q1 specimen employed was entirely, or almost entirely, free from amylases, since in 300 minutes at 21° there was a fall of 75·2% in A.V. (6800 A.), whilst the " apparent conversion into maltose " was only 0·9%.

Stability of the Q1-Enzyme Fraction in Solution.—Samples of fraction Q1 prepared by the standard method from 100 c.c. of potato juice were dissolved in water (20 c.c.) and stored at different temperatures, namely, at 0°, room-temperature (*ca.* 17°), 35·5°, 45·5° and 55·5°. At intervals, a portion (2·5 c.c.) of each solution was incubated with amylose, under the conditions of the standard digest, and the Q-enzyme activity calculated by reference to curves showing the effect of dilution on the activity of the original Q1 solution. The rates of decay of the enzyme in solution at room temperature and at 0° are shown in Fig. 4. Each of the enzyme solutions employed was shown to be essentially free from α- and β-amylases by its ability to effect a fall of 75% in the A.V. (6800 A.) of the amylose, with less than 2% " apparent conversion into maltose."

Freeze-drying of Q-Enzyme Samples.—(a) *Potato juice.* When potato juice was frozen in an alcohol–carbon dioxide mixture and dried at 0·01 mm., very little, if any, loss of Q-enzyme activity occurred. This method of obtaining solid enzyme was unsuitable for routine purposes, because of the large volume of water to be removed in the drying process and the extremely hygroscopic nature of the product.

(b) *The lead–protein complex.* In four experiments, fraction Q1 was prepared from potato juice (100 c.c.) by the standard method, with the exception that the lead–protein complex was freeze-dried, as above, before the elution stage. Each Q1 specimen was dissolved in water (20 c.c.), and its activity determined by reference to the dilution curve (see above). The enzyme samples thus obtained had about 40% of the activity of an average sample of fraction Q1 prepared by the standard method without freeze-drying.

(c) *Fraction Q1.* Fraction Q1, isolated by the standard method from potato juice (100 c.c.), was dissolved in water (20 c.c.) and the solution divided into two equal portions, one of which served as a control. The other was freeze-dried, as above, and the product redissolved in water (10 c.c.). The Q-enzyme contents of the freeze-dried and control enzymes were compared by the method already given. The results obtained with two different samples of Q1 are shown below and are typical of 30 such experiments. Each of these enzyme preparations effected a fall of at least 80% in the A.V. (6800 A.) of amylose, with an " apparent conversion into maltose " of only 1%.

Q-Enzyme.	Treatment.	Fall (%) in A.V. (6800 A.) of amylose (30 mins.).	P-Units from 100 c.c. of juice.
First sample	Control	67·8	14·5
	Freeze-dried	64·7	5·9
Second sample	Control	72·6	—
	Freeze-dried	69·8	—

(d) *Fraction Q3.* The Q3 fraction isolated from potato juice (150 c.c.) was redissolved in water (30 c.c.), and the solution divided into three equal parts, one of which served as a control. The second was freeze-dried, as above, and the third freeze-dried in the presence of potato juice (5 c.c.) ,which had previously been boiled for 10 minutes and centrifuged. The two freeze-dried samples were redissolved in water (10 c.c.). The Q-enzyme activities of the three solutions were measured, as above. The Q3 fraction used in these experiments effected a fall of 80% in the A.V. (6800 A.) of amylose with no detectable increase in reducing power.

Treatment of enzyme solution.	Fall (%) in A.V. (6800 A.) of amylose (30 mins.).	P-Units from 100 c.c. of juice.
Control	70·4	2·6
Freeze-dried	2·8	—
Freeze-dried with boiled juice added	69·0	—

The authors desire to express their thanks to Professor Sir Norman Haworth, F.R.S., for the interest he has taken in this work.

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367. *The Enzymic Synthesis and Degradation of Starch. Part V. The Action of Q-Enzyme on Starch and its Components.*

By S. A. Barker, E. J. Bourne, and Stanley Peat.

The end-product of the action of Q-enzyme on amylose is a red-staining polysaccharide, having a ramified structure and an average chain-length less than that of amylose. This polysaccharide, like that produced from potato starch by Q-enzyme, is indistinguishable from natural amylopectin. The hypothesis of Bourne and Peat (*J.*, 1945, 877) that Q-enzyme catalyses the conversion of amylose into amylopectin is substantiated.

In the preceding paper (Part IV) we recalled that Bourne and Peat (*J.*, 1945, 877) ascribed a dual function to the Q-enzyme of the potato. Like the heat-labile enzyme of heart, liver, and yeast (Cori, Swanson, and Cori, *Federation Proc.*, 1945, **4**, 234), it catalyses, in association with P-enzyme (phosphorylase), the synthesis of amylopectin from glucose-1 phosphate. In addition to playing this rôle in polysaccharide synthesis, Q-enzyme effects the conversion of blue-staining amylose into a red-staining polysaccharide without the concomitant liberation of reducing sugar. When potato starch was used as a substrate for Q-enzyme, a polysaccharide was formed which was closely similar to natural amylopectin with respect to blue value (B.V.) and limiting conversion (57%) into maltose by β-amylase (Bourne, Macey, and Peat, *J.*, 1945, 882). Since little polysaccharide was lost during the experiment, it appeared highly probable that the amylose component of the starch had been converted by the enzyme into amylopectin. At that time no attempt had been made to isolate the red-staining polysaccharide produced by Q-enzyme from amylose itself, and the purpose of the present communication is to report an extension of the earlier work, whereby we have conclusively demonstrated that amylose is indeed transformed by Q-enzyme into amylopectin.

Experimental confirmation of the original hypothesis has had to wait upon the development of an improved method for the isolation of Q-enzyme, in which the main obstacles to be overcome were related to the labile nature of the enzyme and the presence of amylases. Details of the successful purification of Q-enzyme have been given in Part IV. Briefly, Q-enzyme is precipitated with lead acetate and eluted with sodium hydrogen carbonate solution in the presence of carbon dioxide. It is then precipitated (fraction Q1) with neutral ammonium sulphate (19 g./100 c.c.) and can be further purified by re-precipitation (fraction Q3). Both fractions, Q1 and Q3, have been employed in this work.

In Part IV it was shown that an average specimen of the enzyme at the Q1 stage of purification effects (at 20·5° and pH 7·04) a decrease of as much as 87% in the absorption value, A.V. (6800 A.), of amylose (B.V., 1·04) while the reducing power developed corresponds to only 2% conversion of maltose. That this represents the end-point of the reaction is evident from the progress curves in Fig. 1. With this particular Q1 sample the A.V. (6800 A.) decreased 86% in 2 hours and by only 3% more (to 89%) in 20 hours; the " apparent percentage conversion into maltose " was never greater than 4%. The changes in the iodine-staining properties of the polysaccharide are shown by the absorption curves in Fig. 2; the wave-length of peak absorption gradually moved from 6400 A. to 5200 A. as the enzymic reaction proceeded. The latter value is very close to that shown by waxy-maize starch.

The formation of a ramified structure from linear amylose chains was demonstrated by allowing Q-enzyme and β-amylase (from soya-bean) to act simultaneously on amylose. Whereas a highly active solution of β-amylase acting alone on amylose (B.V., 1·30) at pH 7·0 and 20·5° converted 90·2% of the polysaccharide into maltose in 210 minutes, a second portion of the same amylase solution acting together with Q-enzyme (fraction Q1) gave only 74·2% of maltose in the same time. Furthermore, incubation of the amylose with Q-enzyme before the addition of β-amylase resulted in the liberation of even smaller quantities of maltose. Thus, when the amylose was incubated with Q-enzyme for 30, 90, and 180 minutes (thereby decreasing the A.V. by 75, 83, and 87%, respectively) before the introduction of the β-amylase, the limiting conversions into maltose effected by the latter enzyme were 63·0, 57·0, and 55·8%, respectively.

Although these results were in full accord with the hypothesis that Q-enzyme had transformed the unbranched amylose chains into the branched chains of amylopectin, there remained the possibility that a ramified structure had been built up from intact amylose chains without a diminution in the length of the chains. To distinguish between these alternatives, the experiment was repeated with much weaker solutions of β-amylase and attention was directed not to the limiting conversions but rather to the initial rates of maltose production. For, if it is

recognised that β-amylase functions by the end-wise removal of maltose units from polyglucose chains, then the speed of hydrolysis will depend on the number of chain-ends available. It follows that any decrease in average chain-length due to fragmentation of the original amylose chains by Q-enzyme should be revealed by an increase in the initial rate of β-amylolysis. From Fig. 3 it will be seen that the simultaneous action of Q-enzyme and β-amylase increases considerably the rate of maltose production over that of β-amylase acting alone. Pre-treatment

FIG. 1.

Hydrolysis of amylose (B.V., 1·04) by Q-enzyme at 20·5° and pH 7·04.

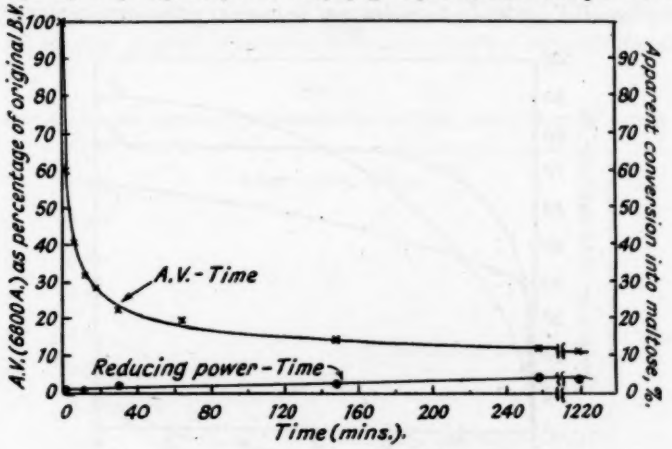
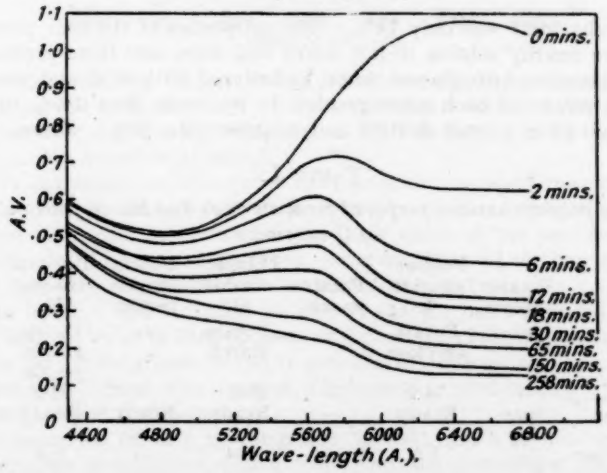


FIG. 2.

Light absorption curves obtained during treatment of amylose (B.V., 1·04) with Q-enzyme at 20·5° and pH 7·04.



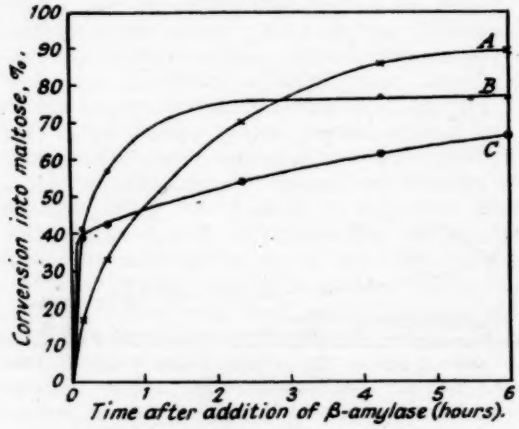
with Q-enzyme is even more effective. Nevertheless, this increase in the rate of β-amylolysis in the presence of Q-enzyme is accompanied by a decrease in the extent of the limiting conversion into maltose. Q-Enzyme is thus shown to have two actions on amylose, namely, scission of the chains and cross-linking of the fragments. These two functions of the enzyme are not necessarily independent and it may well be that scission of each 1 : 4-link in the original polysaccharide chain is accompanied by the simultaneous formation of a branching 1 : 6-link. Such a mechanism would be in keeping with the low reducing powers developed and also with energy requirements. In such circumstances it is not to be expected that appreciable concentrations of short unbranched chains (called pseudo-amylose by Bourne and Peat, *J.*, 1945, 877) would appear during the earlier stages of the incubation. Dr. Shlomo Hestrin, in

a personal communication (June 1948), suggested that a non-hydrolytic exchange of linkage without an intermediate hydrolysis might account for the experimental findings.

In order that a closer study of the products of Q-enzyme action might be made, red-staining polysaccharides (I—IV) were prepared from four different substrates, namely potato-starch, -amylose, and -amylopectin, and waxy-maize starch. The yield of polysaccharide was over 90% in every case except in that when amylose was used as substrate (polysaccharide I). A part of the product from amylose passed through the dialysis membrane and, in consequence,

FIG. 3.

Hydrolysis of amylose (B.V., 1·30) by β-amylase and Q-enzyme, acting simultaneously at pH 7·0 and 20·5°.



A.—β-Amylase alone.
B.—β-Amylase and Q-enzyme added together.
C.—β-Amylase added 1 hour after Q-enzyme.

the yield of polysaccharide I was only 74%. The properties of the four products are listed in Table I. They were readily soluble in hot water and were free from protein. Each showed more than 93% conversion into glucose when hydrolysed with acid and gave less than 0·7% ash. The reducing power of each corresponded to no more than 1·5% of that of maltose. With β-amylase, each gave a limit dextrin and maltose (52—57%), whereas the limiting con-

TABLE I.

The properties of polysaccharides prepared from starches and starch fractions by the agency of Q-enzyme.

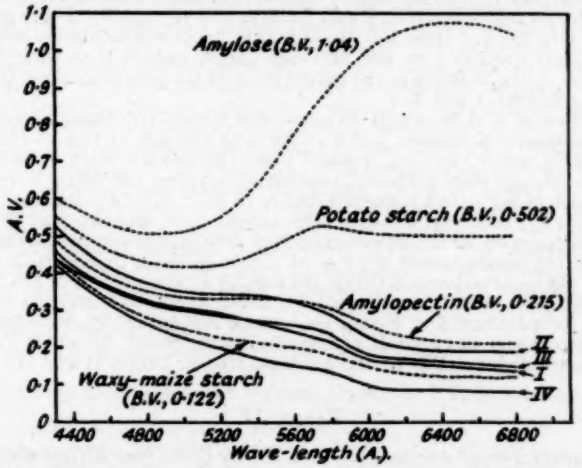
Property.	Potato amylose.	Polysaccharide I.	Potato starch.	Polysaccharide II.	Potato amylopectin.	Polysaccharide III.	Waxy-maize starch.	Polysaccharide IV.
Source	—	Potato amylose	—	Potato starch	—	Potato amylopectin	—	Waxy-maize starch
Yield (%)	—	74·2	—	90·0	—	91·2	—	92·9
Solubility in hot water	Sparing	Ready	—	Ready	Ready	Ready	—	Ready
Reducing power (as percentage of maltose)	—	1·5	—	0·4	—	0·2	—	0·1
Protein tests	—	Negative	—	Negative	—	Negative	—	Negative
Iodine-stain	Blue	Red	Blue	Reddish-purple	Reddish-purple	Red	Red	Red
B.V.	1·04	0·136	0·502	0·189	0·215	0·147	0·122	0·080
Approx. wave-length of peak absorption (A.) (Fig. 4)	6400	5200	5800	5400	5600	5300	5200	5100
Ash (%)	—	0·32	—	0·47	—	0·61	—	0·70
Glucose produced by acid hydrolysis (%)	—	97	—	96	—	>93	—	>93
Limiting amount of maltose produced by β-amylolysis (%)	90	55	69	57	56	52	50	53

versions of the polysaccharides from which they were derived were 90% (amylose), 69% (potato starch), 56% (amylopectin), and 50% (waxy-maize starch).

The blue value of the product was invariably lower than that of the parent polysaccharide, the difference being pronounced when amylose or potato starch was used, but small when amylopectin or waxy-maize starch was employed. The observed fall in B.V. of potato amylopectin and waxy-maize starch was probably due to the conversion into amylopectin of the small amounts of amylose which are known to be present in waxy-maize starch and in potato amylopectin prepared by the " thymol " method (Bourne, Donnison, Haworth, and Peat, *J.*, 1948, 1687; Bourne and Peat, this vol., p. 5). The light-absorption curves of the iodine complexes of polysaccharides I—IV closely follow the curve for natural amylopectin (see Fig. 4). The wave-lengths of peak absorption quoted in Table I were obtained, in the case of

FIG. 4.

Light absorption curves of polysaccharides isolated after Q-enzyme action.



red-staining polysaccharides, by using more concentrated polysaccharide–iodine solutions than are usually employed with amylose. Polysaccharides I—IV exhibited absorption peaks between 5100 and 5400 A., compared with 5600 A. for the sample of " thymol " amylopectin employed and 5200 A. for waxy-maize starch.

It is desirable to emphasise at this point that no claim is made that the polysaccharides I—IV are identical. Indeed Table I shows the contrary. For example, the blue values of the products of Q-action differ and are related to the blue value of the particular substrate from which each was derived. The results do prove, however, that all of these products, whatever their starch source, have the branched-chain amylopectin structure.

These studies, in which a stable, highly purified Q-enzyme has been used, fully substantiate the hypothesis put forward by us in 1945 (Bourne and Peat, *J.*, 1945, 877), namely, that Q-enzyme plays a dual rôle in that it catalyses (i) the fragmentation of long amylose chains and (ii) the synthesis of the branched-chain structure of amylopectin, presumably by the formation of cross linkages between these fragments.

A practical consequence of this investigation is that there is now available, in stable powder form, an enzyme preparation which will effect the conversion not only of amylose, but of any natural starch or mixture of starches wholly into non-retrograding, water-soluble amylopectin.

Since the completion of this work Bernfeld and Meutémédian (*Nature*, 1948, **162**, 297, 618; *Helv. Chim. Acta*, 1948, **31**, 1724, 1735) have described the isolation, from potatoes, of an " isophosphorylase," which in some respects seems to fulfil the same function as Q-enzyme. These authors stipulate, however, that a phosphate transfer is involved in its action We intend to discuss the relation between the two enzymes in a later communication.

EXPERIMENTAL.

Analytical Methods.—The analytical methods employed in this work have already been described in the preceding paper (Part IV).

Fractionation of Starch.—The amylose and amylopectin fractions were derived from potato starch by selective precipitation of the former with thymol, according to the standard procedure of Bourne Donnison, Haworth, and Peat (*J.*, 1948, 1687). Several such fractionations were necessary in order to prepare the purer sample of amylose, which had B.V. 1·30.

Isolation of Q-Enzyme.—The Q1 fraction was isolated from potatoes by treatment with lead acetate, sodium bicarbonate–carbon dioxide, and ammonium sulphate, as described in the previous paper. It was stored at 0° as the powder obtained when a solution was freeze-dried. In some cases this powder was purified before used by reprecipitation with neutral ammonium sulphate (19 g./100 c.c.), giving fraction Q3.

Preparation of β-Amylase.—The β-amylase was isolated from soya-beans by the method of Bourne, Macey, and Peat (*J.*, 1945, 882). There was no increase in reducing power when the enzyme was incubated with maltose in acetate buffer at pH 5·3.

β-Amylolysis of Polysaccharides.—A solution of the dry polysaccharide (20 mg.) in 0·1N-sodium hydroxide (25 c.c.) was exactly neutralised with 0·5N-hydrochloric acid and diluted to 34 c.c. After the addition of acetate buffer (pH 5·3; 6 c.c.) and 0·2% β-amylase solution (10 c.c.), making a total volume of 50 c.c., the digest was incubated at room temperature. At intervals, the reducing power was determined, in terms of maltose, by the Shaffer–Hartmann method (*J. Biol. Chem.*, 1921, **45**, 377), a small correction being made, when necessary, for the reducing power of the enzyme.

Action of Fraction Q1 on Amylose (B.V., 1·04). Measurement of Iodine Stains and Reducing Powers.—A solution of fraction Q1 (20 c.c.; from 100 c.c. of potato juice) was incubated with amylose (B.V. 1·04), as in the standard digest described in the previous paper, except that three-fold quantities of the reagents were employed. The changes in the iodine stain of the polysaccharide and the reducing power of the digest are shown in Figs. 1 and 2.

Hydrolysis of Amylose (B.V. 1·30) by Q1 Fraction and β-Amylase Acting Simultaneously.—(a) *Using a 0·04% β-amylase solution.* A sample (1·6 g., equiv. to 236 c.c. of potato juice) of freeze-dried Q1 fraction was dissolved in water (40 c.c.), a small insoluble residue being removed by the centrifuge. Digests (total volume, 50 c.c.) were prepared, containing amylose (20 mg.; B.V. 1·30; dissolved as in previous paper), maltose (8 mg.), and M-acetate buffer (5 c.c.; pH 7·0), together with 0·2% β-amylase solution (10 c.c.) and/or Q1 solution (5 c.c.). The digests were incubated at 20·5° and, at intervals, aliquot portions were withdrawn for the determination of reducing power and for the measurement of A.V. (6800 A.). For the latter measurement 2·5 c.c. of digest solution (equiv. to 1 mg. of amylose) were stained with iodine (2 mg.) and potassium iodide (20 mg.) in a total volume of 100 c.c. A control sample from which the amylose was omitted was incubated simultaneously with each digest. These controls revealed that the Q1 preparation and β-amylase, acting separately, or together, showed no maltase activity. In each control there was a small, constant reducing power, for which a correction was applied in the corresponding main digest. The results are tabulated in Tables II and III.

TABLE II.

Conversion of amylose (B.V. 1·30) by Q-enzyme acting alone.

Time (mins.).	Apparent conversion into maltose (%).	Fall (%) in A.V. (6800 A.).
0	0	0
30	0·9	75·2
60	—	77·7
90	—	82·7
180	2·8	86·9

TABLE III.

Conversion of amylose (B.V. 1·30) by Q-enzyme and β-amylase, acting together.

Enzymes used.	Time of incubation with Q1 before addition of β-amylase (mins).	Conversion into maltose (%): 30 mins. after addition of β-amylase.	210 mins. after addition of β-amylase.
β-Amylase	—	63·0	90·2
β-Amylase + Q-enzyme ...	0	47·5	74·2
,, ,, ...	30	45·2	63·0
,, ,, ...	90	38·0	57·0
,, ,, ...	180	38·0	55·8

(b) *Using a 0·01% concentration of β-amylase.* The previous experiment was repeated under the same conditions, except that the final concentration of β-amylase was 0·01 instead of 0·04%. The enzyme and amylose specimens were the same as those previously employed. The reducing power was determined at more frequent intervals in order that the initial rates of β-amylolysis could be ascertained. The results are shown graphically in Fig. 3.

Method of Isolation of the Polysaccharides Produced from Starches and their Components by Treatment with Q-Enzyme.—The starch, or starch fraction (2·8 g.), was dissolved, by warming, in 0·5N-sodium hydroxide (150 c.c.). The solution was cooled, diluted with water to *ca.* 1300 c.c., and neutralised to phenolphthalein with N-sulphuric acid. After the introduction of maltose solution (equiv to 0·6 g. of maltose), M-acetate buffer (500 c.c.; pH, 7·04), and Q-enzyme solution (500 c.c.), the digest was diluted with water to 2800 c.c. and kept at room temperature. At intervals, aliquot portions were removed for the determination of reducing power (4 c.c.) and of A.V. (6800 A.). For the latter measurement, the

digest sample (1 c.c., equiv. to 1 mg. of original polysaccharide) was stained with iodine (2 mg.) and potassium iodide (20 mg.) in a total volume of 100 c.c.

When the A.V. (6800 A.) reached a constant value, the reaction was arrested by heating the digest in a boiling water-bath for 1 hour. The solution was cooled and the coagulated protein removed. In the case of polysaccharide I (from amylose), the crude polysaccharide was precipitated with alcohol (3 volumes), ground with alcohol and then with ether, and dried at 60° over phosphoric oxide in a vacuum.

In the other cases the protein-free supernatant liquid was concentrated under reduced pressure to 250 c.c. Each of these solutions, and also a solution of crude polysaccharide I, was dialysed in cellophane against frequent changes of distilled water. The dialysis was continued for 24 hours after the dialysate had ceased to give a precipitate with barium chloride solution. After the addition of a trace of sodium chloride, the polysaccharide was precipitated with alcohol (3 volumes), ground with alcohol and then with ether, and dried at 60° in a vacuum over phosphoric oxide.

(a) *Polysaccharide I from amylose* (*B.V.* 1·04). Fraction Q1, freshly prepared from 2,400 c.c. of potato juice, was dissolved in water (500 c.c.). Initially, half of this solution was added to the digest, the remainder being added after 4 hours. The reaction was terminated after 24 hours, by which time the A.V. (6800 A.) was 0·120 and the " apparent conversion into maltose " was 4·0%. Crude polysaccharide I (11·1 g.) contained 74% of ash, and had B.V. 0·107 (calculated on the assumption that there had been no loss of polysaccharide). During dialysis a small proportion of the polysaccharide passed through the membrane. Polysaccharide I (yield, 74·2%) had B.V. 0·136 and ash, 0·32%.

(b) *Polysaccharide II from potato starch* (*B.V.* 0·502). The Q-enzyme (500 c.c.) used in this digest was at the Q3-stage and had been isolated from 250 c.c. of potato juice and stored at 0° in the freeze-dried Q1-form for 9 weeks. When the digest was stopped after 520 minutes, the A.V. (6800 A.) was 0·195 and the " apparent conversion into maltose " was 2·1%. No iodine-staining material passed through the dialysis membrane. Polysaccharide II (yield, 90·0%) had B.V. 0·189.

(c) *Polysaccharide III from amylopectin* (*B.V.* 0·215). The Q3 fraction (500 c.c.) employed had been prepared from 210 c.c. of potato juice and stored at 0° as freeze-dried Q1 fraction for 14 weeks. The A.V. (6800 A.) and the " apparent conversion into maltose " were 0·135 and 0·7%, respectively, when the digest was inactivated after 7 hours. There was no detectable passage of iodine-staining material during dialysis. Polysaccharide III (yield, 91·2%) had B.V. 0·147.

(d) *Polysaccharide IV from waxy-maize starch* (*B.V.* 0·122). The waxy-maize starch had been defatted with aqueous dioxan and then with aqueous methanol. The Q3 preparation was the same as that used in (c). The digest was stopped after 345 minutes, the A.V. (6800 A.) being 0·107 and the " apparent conversion into maltose " 1·4%. No iodine-staining polysaccharide was lost during dialysis. Polysaccharide IV (yield, 92·9%) had B.V. 0·080.

The properties of these polysaccharides are summarised in Table I.

The authors are indebted to Professor Sir Norman Haworth, F.R.S., for his interest in this work.

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368. *Epimeric Alcohols of the* cyclo*Hexane Series. Part VIII. Inactive 2- and 4-Methyl*cyclo*hexanol.*

By L. M. JACKMAN, A. KILLEN MACBETH, and J. A. MILLS.

Details are given of the separation and purification of the inactive epimers of 2-methyl-*cyclo*hexanol and the epimers of 4-methyl*cyclo*hexanol, with lists of solid derivatives. A useful degree of separation of the epimers in mixtures of the 4-methyl*cyclo*hexanols, as well as the 2-methyl*cyclo*hexanols, may be effected by partial esterification with *o*-nitrobenzoyl chloride.

NEEDING pure samples of the geometrical isomers of the various methyl*cyclo*hexanols as reference compounds in another research, we have investigated the preparation of the epimeric forms of 2- and 4-methyl*cyclo*hexanol; the 3-methyl*cyclo*hexanols have been discussed recently (Macbeth and Mills, *J.*, 1945, 709).

Several investigators have reported the preparation of epimeric 2-methyl*cyclo*hexanols and their solid derivatives, and there is general agreement between the data of Skita and Faust (*Ber.*, 1931, **64**, 2878), Huckel and Hagenguth (*ibid.*, p. 2892), and Vavon, Perlin, and Horeau (*Bull. Soc. chim.*, 1932, **51**, 644). We have prepared the 2-methyl*cyclo*hexanols by somewhat different methods, and our results agree closely with those of Vavon, Perlin, and Horeau. The *cis*- and *trans*-3 : 5-dinitrobenzoates and the trans-o-*nitrobenzoate* are esters through which the alcohols may conveniently be purified. Attempts to separate the piperazine salts of the hydrogen phthalates, on the lines described by Macbeth and Mills (*loc. cit.*) for the 3-methyl-*cyclo*hexanols, were unsuccessful.

The 4-methyl*cyclo*hexanols have been less thoroughly investigated than the 2-methyl*cyclo*-hexanols, and the only papers describing purification of the epimers through solid esters are

those of Gough, Hunter, and Kenyon (*J.*, 1926, 2052) and of Skita and Faust (*loc. cit.*). Our results, which differ considerably from those of the above authors, indicate that the *cis*-epimer has not previously been obtained in a pure state. The *cis*-4-methyl*cyclo*hexanol of Skita and Faust apparently was impure *trans*-4-methyl*cyclo*hexanol, as the melting points of their solid esters are only slightly below that of the *trans*-esters. The *cis*-alcohol of Gough, Hunter, and Kenyon apparently was a mixture and gave a phenylurethane corresponding in melting point to our *trans*-phenylurethane, but a *p*-nitrobenzoate of melting point corresponding to our *cis*-*p*-nitrobenzoate; this is the behaviour to be expected of a mixture containing considerable amounts of each of the epimeric alcohols, in view of the melting points and solubilities of the esters concerned (cf. table).

Properties of the (±)-2-*Methyl*cyclo*hexanols and the* 4-*Methyl*cyclo*hexanols.*

	(±)-2-Methyl*cyclo*hexanols.		4-Methyl*cyclo*hexanols.	
	cis.	*trans.*	*cis.*	*trans.*
$d_4^{20°}$ of alcohol	0·9274	0·9174	0·9173	0·9040
$n_D^{20°}$ of alcohol	1·4649	1·4616	1·4614	1·4561
o-Nitrobenzoate, m. p.	oil	60—60·5°	oil	68—68·5°
p-Nitrobenzoate, m. p.	56—57°	64·5—65°	96°	64—65°
3 : 5-Dinitrobenzoate, m. p.	100—101°	117°	106—107°	142°
Hydrogen phthalate, m. p.	102—104°	124—125°	84—85°	120—121°
Phenylurethane, m. p.	92—93°	105°	103—104°	124—124·5°
α-Naphthylurethane, m. p.	112°	156°	106—107°	159·5—160°

The differences in physical properties of the *cis*- and *trans*-4-methyl*cyclo*hexanols, and in the melting points of their derivatives, were much greater than in the case of the 2- and 3-methyl*cyclo*hexanols, and the *p*-nitrobenzoate of *cis*-4-methyl*cyclo*hexanol showed an abnormally high melting point, but the purity of the epimeric alcohols was proved by regeneration of each epimer from two solid esters, the *cis*-*p*-nitrobenzoate and cis-*hydrogen phthalate*, the *trans*-3 : 5-dinitrobenzoate and cis-o-*nitrobenzoate*.

The physical constants of the epimeric alcohols and their derivatives are given in the table. They are in agreement with the configurations assigned, with the exception of *cis*-4-methyl*cyclo*hexyl *p*-nitrobenzoate.

As in the case of *m*-cresol (Macbeth and Mills, *loc. cit.*), rapid hydrogenation of *o*- and *p*-cresol over Raney nickel definitely favoured the formation of the corresponding *trans*-methyl*cyclo*hexanols, and hydrogenation of 2- and 4-methyl*cyclo*hexanone over Raney nickel at 120—130° gave mixture of alcohols in which the *cis*-epimer was in moderate excess (about 60%).

The separation of *cis*-2-methyl*cyclo*hexanol from large amounts of the *trans*-epimer involved very tedious fractional crystallisations, and an attempt was made to increase the percentage of *cis*-epimer by partial esterification of the mixture. Read and Grubb (*J.*, 1934, 1781) showed that with *p*-nitrobenzoyl chloride menthol (*trans*) reacts at 16·5 times the speed of *neo*menthol (*cis*), and that with *o*-nitrobenzoyl chloride the ratio of rates of reaction is 22·5; these differences were used to effect a separation of menthol and *neo*menthol. Read and co-workers have also used partial esterification to separate mixtures of *iso*menthols (*J.*, 1934, 313) and carvomenthols (*J.*, 1935, 1138). The data given for the separation of the carvomenthols show that the *trans*-configuration of methyl and hydroxyl groups increased the rate of reaction with *p*-nitrobenzoyl chloride about six-fold as compared with the *cis*-configuration. The configuration of methyl and hydroxyl groups found in carvomenthol is also present in 2-methyl*cyclo*hexanol, but for the latter the ratio of rates of reaction of *trans* and *cis* was only about 2 : 1, when using *o*-nitrobenzoyl chloride, which might be expected to show the largest ratio of reactivities. However, this difference in reactivity was sufficient to give a useful enrichment of *cis*-epimer in the mixture from the hydrogenation of 2-methyl*cyclo*hexanone, and its complete purification was then easily effected.

Purification of *cis*-4-methyl*cyclo*hexanol could be carried out without its enrichment in the mixture from hydrogenation, but a partial esterification was carried out on a mixture of *cis*- and *trans*-4-methyl*cyclo*hexanol, with the interesting result that for these two epimers with *o*-nitrobenzoyl chloride the ratio of reactivity of *trans* to that of *cis* is about 2·5 : 1, a ratio at least as great as that found for the 2-methyl*cyclo*hexanols. If the lower rate of reaction of the *cis*-epimer is due only to steric hindrance by the methyl group, the hindering effect is equally as great when the methyl group is in position 4 to the hydroxyl as when it is in position 2. The introduction of an *iso*propyl group at position 5, as in carvomenthol, accentuates the difference

in reactivity associated with the 2-methyl group. (For the method of calculating the ratios, see the article by Read and Grubb, *loc. cit.*)

3 : 5-Dinitrobenzoyl chloride was prepared by the use of pyridine and a molar proportion of thionyl chloride (cf. Human and Mills, *Nature*, **1946**, **158**, 877), and the solution so obtained was used directly for preparation of 3 : 5-dinitrobenzoates without isolation of the chloride.

Experimental.

(±)-trans-2-*Methyl*cyclo*hexanol*.—Purified *o*-cresol (187 g.) was hydrogenated over Raney nickel (3 g.), reaction commencing at 150°/2600 lb. and being complete after 3·5 hours at 180°. Removal of the catalyst, and distillation *in vacuo*, gave a mixture of 2-methyl*cyclo*hexanols (170 g.), $d_4^{20°}$ 0·9206 (68% *trans*).

Dry, powdered 3 : 5-dinitrobenzoic acid (50 g.) was mixed with anhydrous pyridine (40·5 g., 2·2 moles) and anhydrous benzene (100 ml.), and the suspension cooled. With thorough stirring and exclusion of moisture, pure thionyl chloride (25·6 g., 1·0 mole) in benzene (80 ml.) was dropped in during 30 minutes, the temperature being maintained below 30°. The solution was then boiled for 10 minutes. The mixture of 2-methyl*cyclo*hexanols (25·7 g., 1·0 mole) obtained above, dissolved in benzene (80 ml.), was added during a period of 40 minutes, with stirring and cooling to below 30°. The solution was then heated under reflux for an hour and kept at room temperature overnight. Removal of pyridine hydrochloride and free 3 : 5-dinitrobenzoic acid in the usual way was followed by steam-distillation of the benzene solution. The mixture of 3 : 5-dinitrobenzoates so obtained solidified readily on cooling; m. p. 70—80° (85% yield). A systematic three-stage crystallisation from 95% alcohol gave, after five crystallisations, a 43% recovery of pure (±)-*trans*-2-methyl*cyclo*hexyl 3 : 5-dinitrobenzoate, as fine pale yellow needles, m. p. 117°. The pure ester was hydrolysed by heating under reflux for 30 minutes with a 5% solution of potassium hydroxide (1·3 moles) in methyl alcohol. Working up in the usual way, followed by continuous extraction of the aqueous steam-distillate with light petroleum (b. p. 40—60°), gave pure (±)-*trans*-2-methyl*cyclo*hexanol, b. p. 53°/3·5 mm. (85%).

Of the derivatives listed in the table, the *p*-nitrobenzoate (plates) was recrystallised from aqueous methyl alcohol, the hydrogen phthalate (granules), phenylurethane (rosettes), and α-naphthylurethane (fine needles) from light petroleum. The melting points of these derivatives, and all others for which no analyses are given, agree closely with values in the literature.

(±)-cis-2-*Methyl*cyclo*hexanol*.—The mixture of 2-methyl*cyclo*hexanols resulting from the hydrogenation of *o*-cresol was oxidised by the method used by Macbeth and Mills (*loc. cit.*) for 3-methyl*cyclo*hexanol, giving (±)-2-methyl*cyclo*hexanone, $d_4^{20°}$ 0·9160, in 80% yield.

This ketone (50 g.) was hydrogenated over Raney nickel (3 g.) at 130°/2300 lb., the reduction requiring 2·5 hours. From the product, (±)-2-methyl*cyclo*hexanol, free of ketone, was recovered in 92% yield; it had $d_4^{20°}$ 0·9231 (57% *cis*).

The following procedure doubled the ratio of *cis*- to *trans*-epimer in the mixture. Pure *o*-nitrobenzoic acid was converted into the chloride by thionyl chloride under the conditions recommended by Bonner and Hurd (*J. Amer. Chem. Soc.*, 1946, **68**, 344). The (±)-2-methyl*cyclo*hexanol (57% *cis*) (49 g.) was dissolved in anhydrous pyridine (200 ml., 5·7 moles) and stirred vigorously while a solution of *o*-nitrobenzoyl chloride (from 50 g. of acid, 0·7 mole) in benzene (40 ml.) was added during 1·5 hours at <25°. The solution of *o*-nitrobenzoyl chloride gave a dark-blue insoluble solid if allowed to react with pyridine in the absence of excess of alcohol and must thus be dropped into the pyridine solution without splashing on the walls of the flask. After the mixture had been kept at 25—30° overnight, pyridine was removed by pouring it into hydrochloric acid containing crushed ice, the acidic solution was extracted with ether, and the extracts were washed with dilute alkali, followed by water. The ether, benzene, and unesterified alcohol were steam-distilled from the mixed *o*-nitrobenzoates, and from the distillate (±)-2-methyl*cyclo*hexanol was recovered (12·5 g., 77%), $d_4^{20°}$ 0·9251 (77% *cis*).

This alcohol was esterified with 3 : 5-dinitrobenzoic acid by the method described above, giving a crude ester with m. p. 70—75° (88% yield). A six-fold systematic recrystallisation from 95% alcohol gave (±)-*cis*-2-methyl*cyclo*hexyl 3 : 5-dinitrobenzoate as fine, pale yellow needles, m. p. 100—101° (55% recovery). Hydrolysis of this ester gave pure (±)-*cis*-2-methyl*cyclo*hexanol, b. p. 50·5°/2·9 mm. (80%).

Physical properties are listed in the table. The *p*-nitrobenzoate (pale needles) was recrystallised from aqueous methyl alcohol, the hydrogen phthalate (rosettes) and the phenylurethane (fine needles) from light petroleum. The *α-naphthylurethane* was obtained as felted white needles from light petroleum (Found : N, 5·0. $C_{18}H_{21}O_3N$ requires N, 5·0%).

The mixed *o*-nitrobenzoates obtained in the partial esterification were placed in a refrigerator, where they slowly became partly solid. Washing out of oil by ice-cold light petroleum (b. p. 40—60°), followed by several recrystallisations of the solid from light petroleum, gave pure (±)-trans-2-*methyl*cyclo*hexyl* o-*nitrobenzoate* (19 g.) as large yellow rhombs, m. p. 60—60·5° (Found : N, 5·4. $C_{14}H_{17}O_4N$ requires N, 5·3%). Hydrolysis of this ester with methanolic potassium hydroxide gave (±)-*trans*-2-methyl*cyclo*hexanol with the same density, $d_4^{20°}$ 0·9174, as the product from the 3 : 5-dinitrobenzoate.

trans-4-*Methyl*cyclo*hexanol*.—Pure *p*-cresol was hydrogenated under conditions similar to those used for *o*-cresol and gave a 91% yield of 4-methyl*cyclo*hexanol, $d_4^{20°}$ 0·9069 (82% *trans*).

The alcohol was esterified with pure 3 : 5-dinitrobenzoyl chloride, giving a nearly theoretical yield of ester, m. p. 103—120°, which after five crystallisations from light petroleum (b. p. 80—140°, 8 ml./g.) was obtained as pure *trans*-4-methyl*cyclo*hexyl 3 : 5-dinitrobenzoate, fine pale yellow needles, m. p. 142° (47% recovery). Hydrolysis of the 3 : 5-dinitrobenzoate in the usual way gave an 85% yield of *trans*-4-methyl*cyclo*hexanol, b. p. 54°/3 mm.

The *p*-nitrobenzoate (plates) was recrystallised from aqueous methanol, the hydrogen phthalate (rectangular prisms) and the phenylurethane (flat plates) from light petroleum. The *α-naphthylurethane* was obtained after crystallisation from light petroleum as white felted crystals (Found : N, 5·0%).

cis-4-*Methyl*cyclo*hexanol*.—Oxidation of 4-methyl*cyclo*hexanol by the method used for 2-methyl-

*cyclo*hexanol gave 4-methyl*cyclo*hexanone, $d_4^{20°}$ 0·9072, in 86% yield. Hydrogenation of this ketone over Raney nickel at 125—130° gave in 93% yield a 4-methyl*cyclo*hexanol, $d_4^{20°}$ 0·9118 (59% cis).

Esterification of the alcohol with a slight excess of *p*-nitrobenzoyl chloride gave a crude *p*-nitrobenzoate, m. p. 60—68° (95%). Fractional crystallisation five times from methyl alcohol (95%, 5 ml./g.) yielded pure *cis*-4-methyl*cyclo*hexyl *p*-nitrobenzoate, thin pale yellow laths, m. p. 96° (34% recovery) (Found: N, 5·2. Calc. for $C_{14}H_{17}O_4N$: N, 5·3%), hydrolysis of which gave pure *cis*-4-methyl*cyclo*hexanol, b. p. 52°/2 mm., $d_4^{20°}$ 0·9173, $n_D^{20°}$ 1·4614 (87% yield).

The pure *cis*-alcohol was characterised by the preparation of the 3 : 5-*dinitrobenzoate*, large yellow needles from light petroleum (Found: N, 8·8. $C_{14}H_{16}O_8N_2$ requires N, 9·1%), the *phenylurethane*, fine white needles from light petroleum (Found: N, 6·1. $C_{14}H_{19}O_2N$ requires N, 6·0%), and the *α-naphthylurethane*, white granules from light petroleum (Found: N, 5·0%).

The *hydrogen phthalate* was made in 93% yield from the *cis*-4-methyl*cyclo*hexanol obtained above, by heating it with phthalic anhydride (1·1 moles) in pyridine (2·5 moles) for four hours at 50—60°. One crystallisation of the crude ester from light petroleum (b. p. 60—90°) gave white, chunky crystals, m. p. 84—85° (Found: neut. equiv., 261. $C_{15}H_{18}O_4$ requires neut. equiv., 262). Three more recrystallisations from the same solvent caused no change in melting point, and hydrolysis at this stage regenerated an alcohol with $d_4^{20°}$ 0·9174, which was converted into a *p*-nitrobenzoate, m. p. 96°.

Separation of 4-*Methyl*cyclo*hexanols by Partial Esterification.*—A mixture of *cis*- and *trans*-4-methyl*cyclo*hexanol (91 g.), $d_4^{20°}$ 0·9084 (33% *cis*), was esterified with the acid chloride prepared from *o*-nitrobenzoic acid (100 g., 0·75 mole), by the method used for the partial esterification of 2-methyl*cyclo*hexanol. Unesterified alcohol was recovered (16·5 g., 72%), $d_4^{20°}$ 0·9116 (57% *cis*). The mixture of *o*-nitrobenzoates obtained was set aside until partial solidification occurred, and worked up by the method used for the 2-methyl*cyclo*hexyl esters, yielding pure trans-4-*methyl*cyclo*hexyl o-nitrobenzoate* (56 g., 49%) as large pale yellow rhombs, m. p. 68°, from light petroleum (Found: N, 5·2%). Hydrolysis of this ester gave *trans*-4-methyl*cyclo*hexanol, $d_4^{20°}$ 0·9041.

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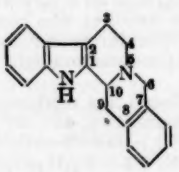
369. *The Constitution of Yohimbine and Related Alkaloids. Part III. The Structure of Sempervirine and Some Further Observations on the Structure of Ketoyobyrine.*

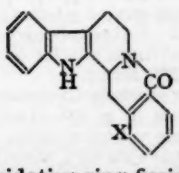
By G. A. SWAN.

A compound having the structure (I) assigned to sempervirine by Prelog *et al.* is synthesised; it differs from the alkaloid in both physical and chemical properties. Both the ketoyobyrine and the synthetic product previously (this vol., p. 110) held to be identical with it are now considered to be mixtures.

GOUTAREL, JANOT, and PRELOG (*Experientia*, 1948, **4**, 24) and Prelog (*Helv. Chim. Acta*, 1948, **31**, 588) recently suggested structure (I) for sempervirine, one of the alkaloids of *Gelsemium sempervirens*. As (II) and (III) have already been synthesised (*J.*, 1946, 618; this vol., p. 110; Schlittler and Allemann, *Helv. Chim. Acta*, 1948, **31**, 128), further work has been directed towards the synthesis of 3 : 4-*dihydro*-7 : 8-*benzindolo*(2′ : 3′-1 : 2)*pyridocoline* (I).



(I.) Double bond at $C_{(9)}$—$C_{(10)}$.
(III.) As formula.
(VIII.) Double bond at $C_{(3)}$—$C_{(4)}$.



(II.) X = H; double bond at $C_{(9)}$—$C_{(10)}$.
(X.) X = Me; double bond at $C_{(9)}$—$C_{(10)}$.
(XI.) X = Me; double bond at $C_{(3)}$—$C_{(4)}$.
(XII.) X = Me; double bonds at $C_{(3)}$—$C_{(4)}$ and $C_{(9)}$—$C_{(10)}$.

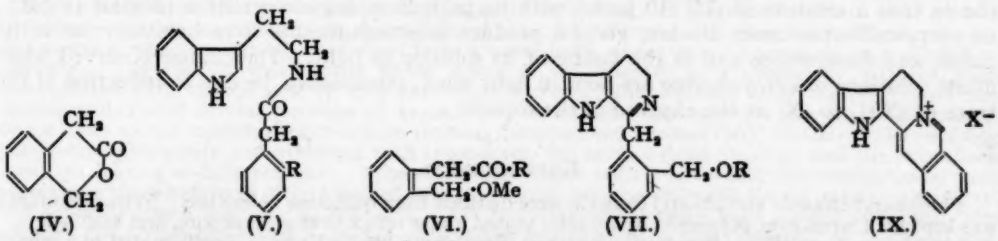
The oxidative ring-fission of cyclic ketones by Caro's acid, previously studied by Baeyer and Villiger (*Ber.*, 1899, **32**, 3625; 1900, **33**, 858), Robinson and Smith (*J.*, 1937, 371), and others, has now been extended to indan-2-one which furnished iso*chroman*-3-*one* (IV) in good yield. This lactone with tryptamine yielded a neutral product which appears to be 3-(2′-o-*hydroxymethyl*-

phenylacetamidoethyl)indole (V; R = CH_2·OH), which was also obtained by reduction of (V; R = CO_2Me) with lithium aluminium hydride but which could not be cyclised to (I).

Attention was therefore directed to the synthesis of 3-(2′-*o*-methoxymethylphenylacetamidoethyl)indole (V; R = CH_2·OMe). *iso*Chroman-3-one with methyl sulphate and 50% potassium hydroxide solution gave *methyl* o-*methoxymethylphenylacetate* (VI; R = OMe), which was hydrolysed by alkali to the *acid* (VI; R = OH). Treatment with thionyl chloride then furnished the *chloride* (VI; R = Cl), which condensed with tryptamine to give a gum, presumably (V; R = CH_2·OMe); with phosphoryl chloride this furnished a small yield of a base, m. p. 214—215°; analysis, agreeing with $C_{19}H_{18}ON_2$ or $C_{20}H_{20}ON_2$, and the ultra-violet absorption spectrum, which shows considerable resemblance to that of harmaline (Pruckner and Witkop, *Annalen*, 1943, **554**, 127) suggest that this compound is (VII; R = H) or (VII; R = Me). The amounts obtained have, so far, been too small for attempts at cyclisation to (I).

Synthesis of (I) in good yield was finally realised by reducing (II) with lithium aluminium hydride. The reduction of amides to amines by this reagent was first described by Ehrlich (*J. Amer. Chem. Soc.*, 1948, **70**, 2286), and the reduction of (±)-oxysparteine to (±)-sparteine has been recorded by Clemo, Raper, and Short (*Nature*, 1948, **162**, 296). (I) separates from aqueous alcohol in golden-yellow leaflets, m. p. 210—215° (decomp.), darkening at 190°, and undoubtedly differs from sempervirine, m. p. 228° (from chloroform) or 258° (from aqueous alcohol). The intense blue-violet fluorescence of salts of the latter is here quite absent, although solutions of the base show a faint greenish fluorescence under ultra-violet irradiation. The ultra-violet absorption of the synthetic compound differs from that recorded by Prelog (*loc. cit.*) for sempervirine; and, although there is some difference in the spectra in neutral and alkaline solutions, this change is not so great as in the case of the alkaloid, and, in particular, there is no strong band at λ *ca.* 2900.

The p*K* for (I) could not be determined by electrometric titration of its hydrochloride with sodium hydroxide as, even in water containing 20% of alcohol, precipitation occurred after only a drop or two of alkali had been added. However, it is evident that this is a very much weaker base than sempervirine, for which Prelog quotes p*K* ~10·6 in water.



(IV.) (V.) (VI.) (VII.) (IX.)

Hydrogenation of (I) in the presence of Adams's catalyst in glacial acetic acid, gave (III), identical with the product obtained previously (Part I); the new method is far superior and may be of value in further work in this field, *e.g.*, for synthesis of deoxyyohimbol (Witkop, *Annalen*, 1943, **554**, 83). Moreover, (III) can be further hydrogenated in presence of platinic oxide in acetic acid containing a drop of concentrated sulphuric acid (cf. Kindler and Kwok, *Annalen*, 1943, **554**, 9, and Witkop, *J. Amer. Chem. Soc.*, 1948, **70**, 2617). The absorption of a further 3 moles of hydrogen seems to indicate hydrogenation of the benzene ring of the tetrahydro*iso*quinoline part of the molecule, and further work along these lines is planned.

In alcohol, in the presence of palladised charcoal, no hydrogenation of (I) occurred, but reduction by hydriodic acid gave (III). Forsyth, Marrian, and Stevens (*J.*, 1945, 579) recovered sempervirine as its hydriodide after boiling it for 30 hours with hydriodic acid (*d* 1·7) and red phosphorus, whilst, on hydrogenation, 3 moles of hydrogen were absorbed over palladium and 5 moles in all over Adams's catalyst. Even if Prelog's suggested structure were modified to (VIII), it is difficult to see how this could accommodate these results.

The structure of sempervirine has also been investigated in another manner. If Prelog's structure were correct, one might expect to be able to oxidise the alkaloid with iodine to 3 : 4-*dihydro*-7 : 8-*benzindolo*(2′ : 3′-1 : 2)*pyridocolinium iodide* (IX; X = I) (cf. the oxidation of tetrahydropalmatine to palmatine iodide; Haworth, Koepfli, and Perkin, *J.*, 1927, 548). Accordingly, compounds (I), (III), and sempervirine were each treated with iodine and potassium acetate in alcoholic solution. From (I) and (III), a product, apparently (IX; X = I), crystallising in golden-yellow needles, was obtained. However, from the alkaloid, sempervirine hydriodide was recovered; again, even if structure (VIII) were correct, one might have expected

oxidation with iodine to occur. The iodide (IX; X = I) is a very sparingly soluble compound, but silver chloride in aqueous alcohol gave the more soluble corresponding *chloride* (IX; X = Cl); on hydrogenation over Adams's catalyst in glacial acetic acid this absorbed 2 moles of hydrogen with the formation of (III) (as the hydrochloride) but in alcohol containing slightly more than 1 mole of sodium hydroxide only 1 mole of hydrogen was absorbed, with the formation of (I).

The absorption spectra suggest that the action of light on a solution of (I) involves oxidation to a product such as (IX; probably X is OH).

Ketoyobyrine. The properties of a substance formulated as (XI) (Part II; this vol., p. 110) agree with those described for ketoyobyrine, and were unchanged after crystallisation first from glacial acetic acid and then three times from alcohol. There seemed every reason to believe that this product and ketoyobyrine were both homogeneous and were identical, and it was tentatively suggested that they had structure (XI). This has now been shown to be untenable, as the reduction, by lithium aluminium hydride, of the analogous product of the action of Raney nickel on (II) gives mainly (I), together with a red compound in amount too small to allow of further investigation. Moreover, Woodward and Witkop (*J. Amer. Chem. Soc.*, 1948, **70**, 2409) have shown that on heating ketoyobyrine with palladium at 280°, 1 mole of hydrogen is evolved, with the formation of (XII), a yellowish-green compound of very low solubility, whose solutions exhibit a powerful fluorescence similar to that of ketoyobyrine. Also Schlittler and Speitel indicated that they experienced difficulty in establishing the identity of synthetic (X) (*Helv. Chim. Acta*, 1948, **31**, 1199) with ketoyobyrine (even after chromatography, there was still some difference in the colour of the products). The synthesis of (X) has also been recorded by Julian, Karpel, Magnani, and Meyer (*J. Amer. Chem. Soc.*, 1948, **70**, 2834), and Raymond-Hamet (*Compt. rend.*, 1948, **226**, 137) has put forward the structure (X) for ketoyobyrine on the grounds of similarity in the ultra-violet absorption spectrum to that of ruteacarpine.

In the light of the above work, it is now suggested that in the form usually obtained, ketoyobyrine is not homogeneous, but consists essentially of (X), contaminated by traces of (XII). The Raney-nickel treatment no doubt dehydrogenates a small amount of (X) to (XII), and hence the product appears to be identical with ketoyobyrine. In support of this, it has been shown that a mixture of (II) (10 parts) with its palladium-dehydrogenation product (1 part), on recrystallisation from alcohol, gives a product indistinguishable from ketoyobyrine in its colour and fluorescence and in the fading of its solution in light. The change observed when dilute solutions of ketoyobyrine are kept in light must, presumably, be due to reduction of the trace of (XII) to (X) at the expense of the solvent.

Experimental.

Phosphoryl chloride and thionyl chloride were distilled from quinoline before use. Tetrahydrofuran was kept for 1 week over potassium hydroxide, heated under reflux over sodium wire, and distilled.

iso*Chroman*-3-*one* (IV).—Powdered potassium persulphate (85·7 g.) was gradually added to a stirred mixture of sulphuric acid (121 c.c., *d* 1·8) and water (41 c.c.), followed by absolute alcohol (170 c.c.), the temperature being maintained below 15° throughout. Then, during 1 hour, a solution of indan-2-one (Read and Hurst, *J.*, 1922, **121**, 2550) (20·6 g.) in absolute alcohol (170 c.c.) was added at −2° to +3°. The mixture was stirred for a further 30 minutes at *ca.* +3° and then for 1½ hours during which the temperature was allowed to rise slowly to 18°. Water (1 l.) was added, the product extracted with chloroform, the extract washed with sodium hydrogen carbonate solution, and dried (Na_2SO_4); the solvent was removed and the residual oil stirred with light petroleum (b. p. 40—60°), whereupon it rapidly crystallised. The resulting solid (21 g.) was collected, washed with light petroleum (b. p. 40—60°), and recrystallised from light petroleum (b. p. 80—100°), affording iso*chroman*-3-*one* as colourless leaflets, m. p. 82—83°, b. p. 130°/1 mm. (Found: C, 72·9; H, 5·65. $C_9H_8O_2$ requires C, 73·0; H, 5·4%).

3-(2′-o-*Hydroxymethylphenylacetamidoethyl*)*indole* (V; R = CH_2·OH).—(*a*) The lactone (0·3 g.) and tryptamine (0·32 g.) were heated for 1 hour at 180—190°. After cooling, the *product* was stirred with benzene, filtered off, and recrystallised from methanol (charcoal), affording colourless plates or prisms (0·3 g.), m. p. 163—164° (after drying at 140°/1 mm.) (Found: C, 74·35; H, 6·5; N, 8·85. $C_{19}H_{20}O_2N_2$ requires C, 74·0; H, 6·5; N, 9·1%). (*b*) The lactone (0·16 g.) and tryptamine (0·18 g.) were heated under reflux in dry benzene (5 c.c.) for 6 hours. After cooling, the product (0·24 g.) was collected and crystallised as in (*a*). (*c*) The ester-amide (V; R = CO_2Me) (0·1 g.) in dry benzene (1 c.c.) was treated with lithium aluminium hydride (Finholt, Bond, and Schlesinger, *J. Amer. Chem. Soc.*, 1947, **69**, 1199) (30 mg.) in ether (0·7 c.c.). After being heated under reflux for 3 hours, the solution was cooled, treated with water and dilute hydrochloric acid, and extracted with chloroform. The extract was washed with dilute sodium hydroxide solution and dried (K_2CO_3), the chloroform removed, and the residue recrystallised from methanol, affording the product (70 mg.) as colourless plates, m. p. 163—164°, not depressed by admixture with that obtained in (*a*).

Attempted Cyclisation of the Above Amide.—The amide (50 mg.) was heated under reflux for 1 hour, in an atmosphere of nitrogen, with phosphoryl chloride (1 c.c.), the latter removed by distillation (water-bath; reduced pressure), and the residue treated with dilute hydrochloric acid and extracted with chloroform. The acid layer was filtered, basified (40% NaOH), and extracted with chloroform, the extract dried

(K_2CO_3), and the solvent removed. The residue was negligible. A similar result was obtained after boiling for 4½ hours with phosphoryl chloride.

o-*Methoxymethylphenylacetic Acid* (VI; R = OH).—A solution of potassium hydroxide (4 g.) in water (4 c.c.) was prepared. The above lactone (3 g.) was dissolved in one third of this, and the resulting solution stirred vigorously with water-cooling. Purified methyl sulphate (2 c.c.) was added gradually during 5 minutes; then the remainder of the potassium hydroxide solution and further methyl sulphate (4 c.c.) were added gradually and simultaneously during 20 minutes. After being stirred for a further 1 hour, the mixture was heated under reflux for 1 hour with 30% aqueous sodium hydroxide (6 c.c.) and methanol (20 c.c.). The bulk of the methanol was removed by distillation (water-bath), and the residue dissolved in water, cooled, extracted with ether, acidified (hydrochloric acid), and again extracted with ether. Evaporation of the latter extract after drying (Na_2SO_4) gave an oil (2 g.), which soon solidified. Recrystallised from light petroleum (b. p. 40—60°), this afforded the *acid* (1·5 g.) as colourless prisms or needles, m. p. 53—54° (Found: C, 67·0; H, 6·75. $C_{10}H_{12}O_3$ requires C, 66·7; H, 6·7%). Acidification of the remaining reaction mixture yielded unchanged lactone (0·7 g.).

By omitting the treatment with methanolic sodium hydroxide, the *methyl* ester (VI; R = OMe) was obtained, by extracting with ether, washing the extract with dilute sodium hydroxide solution, drying (K_2CO_3), removing the ether, and distilling the residue, as a colourless mobile liquid, b. p. 108°/1 mm. (Found: C, 68·15; H, 7·35. $C_{11}H_{14}O_3$ requires C, 68·05; H, 7·2%).

o-*Methoxymethylphenylacetyl Chloride* (VI; R = Cl).—To a solution of the above acid (1·55 g.) in dry ether (5 c.c.), thionyl chloride (1·7 g.), followed by dry pyridine (1 drop), was added. After 14 hours at room temperature, the ether was removed (reduced pressure; room temperature) and the residue distilled rapidly, giving the *chloride* (1·52 g.) as a colourless liquid, b. p. 108°/1 mm. (Found: C, 60·1; H, 5·35. $C_{10}H_{11}O_2Cl$ requires C, 60·45; H, 5·55%). Slow distillation from a bath led to partial cyclisation to give the original lactone.

Condensation of the Above Chloride with Tryptamine and Attempted Cyclisation of the Product.—The chloride (0·4 g.) in benzene (5 c.c.) was added during 20 minutes to a vigorously stirred suspension of tryptamine (0·35 g.) in benzene (12 c.c.) and 0·5N-sodium hydroxide (4 c.c.). After being stirred for a further 20 minutes, the aqueous layer was made alkaline by the addition of a little more sodium hydroxide solution, the layers were separated, and the aqueous layer was extracted with ether. The combined ether–benzene extract was washed successively with dilute sodium hydroxide solution, dilute hydrochloric acid, and again dilute sodium hydroxide, and dried (K_2CO_3), and the solvents were removed. The resulting gum failed to crystallise. A benzene solution of it was poured through a column of alumina, and the latter washed through with much benzene, the filtrate being discarded. A mixture of benzene and alcohol (200 : 1) was then run through the column, the filtrate collected in 5 fractions, and each evaporated. Fractions (1) and (5) yielded only small residues and were discarded. Fractions (2), (3), and (4) yielded clear, pale yellow gums which failed to crystallise. These were combined (0·57 g.) and heated under reflux for 1 hour in an atmosphere of pure, dry nitrogen with phosphoryl chloride (8 c.c.). The chloride was removed by distillation from a water-bath, under reduced pressure, in a current of nitrogen. The residue was heated under reflux for 10 minutes in a current of nitrogen with concentrated hydrochloric acid (2 c.c.) and water (15 c.c.), the aqueous layer decanted, and the residue boiled with several portions of water. The combined acidic aqueous extract (total volume, 50 c.c.) was cooled rapidly, decanted from resinous material, and basified (30% NaOH). The resulting pale yellow precipitate was extracted with chloroform, the extract dried (K_2CO_3), and the chloroform removed, leaving a dark red gum. When this was stirred with a little cold chloroform, some solid separated; this was filtered off and washed with chloroform, giving a pink solid (50 mg. in one experiment; but generally much less), m. p. 200—210°. On recrystallisation twice from alcohol (charcoal), this afforded creamy-white needles, m. p. 214—215° (after drying at 80°/1 mm.) (Found: C, 78·65; H, 6·3. $C_{19}H_{18}ON_2$ requires, C, 78·6; H, 6·2. $C_{20}H_{20}ON_2$ requires C, 78·95; H, 6·6%). Light absorption in ethanol: $\lambda_{max.}$ 3230 A., log ε 4·11; $\lambda_{min.}$ 2730 A., log ε 3·42.

3 : 4-*Dihydro*-7 : 8-*benzindolo*(2′ : 3′-1 : 2)*pyridocoline* (I).—A solution of (II) (0·2 g.) in tetrahydrofuran (22 c.c.) was added to one of lithium aluminium hydride (0·13 g.) in ether (3·5 c.c.), and the mixture heated under reflux in an atmosphere of pure, dry nitrogen for 3 hours (water-bath). After being cooled, the reaction mixture was decomposed by the addition of water and acidified (HCl), and the tetrahydrofuran distilled off on a water-bath. On cooling, the clear solution deposited yellow needles, which were collected, washed with water, and recrystallised from boiling water, affording the *hydrochloride* (0·2 g.) as bright yellow needles. For analysis, this was dried for 3 hours at 100°/1 mm., whereafter it formed an orange-coloured powder, m. p. 298° (decomp.) (Found: C, 69·55; H, 5·5. $C_{19}H_{17}N_2Cl,H_2O$ requires C, 69·6; H, 5·8%). A solution of this in hot water was basified (NaOH), cooled, and the resulting solid (0·15 g.) filtered off, washed with water and recrystallised from aqueous alcohol (charcoal), affording the *base* as glittering, golden-yellow leaflets, m. p. 210—215° (decomp.), darkening at 190° (Found, after drying at 80°/1 mm.: C, 82·9; H, 5·8. $C_{19}H_{16}N_2$ requires C, 83·8; H, 5·9%). Light absorption in ethanol: (*a*) freshly prepared solution, $\lambda_{max.}$ 3520 A., log ε 4·46; 2430A., log ε 4·36; $\lambda_{min.}$ 2670 A., log ε 3·68 (this solution is almost colourless and stable in the dark, but when kept in daylight rapidly develops a yellow colour); (*b*) after 2 hours in daylight, $\lambda_{max.}$ 3510, 2520, and 2380 A., log ε 4·44, 4·48, and 4·48, respectively; $\lambda_{min.}$ 2720, and 2460 A., log ε 3·79, and 4·45, respectively; (*c*) after more prolonged action of light, $\lambda_{max.}$ 3510, 2800, 2520, and 2380 A., log ε 4·44, 395, 4·48, and 4·48, respectively; $\lambda_{min.}$ 3000, 2700, and 2460 A., log ε 3·72, 3·83, and 4·45, respectively. Light absorption in 0·01N-NaOH in ethanol: $\lambda_{max.}$ 3518 and 2300 A., log ε 4·45 and 4·46, respectively; $\lambda_{min.}$ 2780 A., log ε 3·67.

3 : 4 : 6 : 9-*Tetrahydro*-7 : 8-*benzindolo*(2′ : 3′-1 : 2)*pyridocoline* (III).—(*a*) The above crude base (0·2 g.) was hydrogenated with previously reduced Adams's catalyst (50 mg.) in glacial acetic acid (15 c.c.) at room temperature and pressure (H_2 absorption: 1 mole in 20 minutes). After filtration from the catalyst, the solvent was removed (water-bath; reduced pressure), the residue basified (dilute sodium hydroxide solution) and extracted with ether, the extract dried (K_2CO_3), the ether removed, and the residue recrystallised from benzene–light petroleum (charcoal), affording the base (0·17 g.) as colourless needles, m. p. 196—197°, not depressed by a specimen prepared by the method described in Part I

(Found: C, 82·6; H, 6·75. Calc. for $C_{19}H_{18}N_2$: C, 83·2; H, 6·6%). (*b*) The same product was also obtained by reduction with hydriodic acid (*d* 1·7) and red phosphorus (heated under reflux for 4 hours), followed by basification.

Action of Iodine on 3 : 4 : 6 : 9-*Tetrahydro*-7 : 8-*benzindolo*-(2′ : 3′-1 : 2)-*pyridocoline.*—A warm solution of potassium acetate (0·7 g.) and iodine (0·35 g.) in absolute alcohol (10 c.c.) was added to one of the base (70 mg.) in alcohol (2 c.c.). The mixture was warmed on the water-bath for 5 minutes and then allowed to cool. The product was filtered off, washed with alcohol, suspended in hot water, treated with sulphur dioxide, filtered off, and washed with water and alcohol; it (0·1 g.) crystallised from alcohol as a felted mass of golden-yellow needles, m. p. 333° (decomp.) (Found: C, 57·1; H, 3·95. $C_{19}H_{15}N_2I$ requires C, 57·3; H, 3·8%). Light absorption in ethanol: $\lambda_{max.}$ 3520, 2810, 2520, and 2390 A., log ε 4·51, 3·97, 4·53, and 4·53, respectively; $\lambda_{min.}$ 2990, 2690, and 2470 A., log ε, 3·73, 3·84, and 4·48, respectively. This *iodide* (IX; X = I) (0·1 g.) was heated under reflux for 13 hours with excess of freshly prepared silver chloride in a mixture of alcohol (100 c.c.) and water (50 c.c.), the filtered liquid was evaporated to dryness (water-bath; reduced pressure), and the residue recrystallised from alcohol, affording the *chloride* (IX; X = Cl) as large orange-red needles (70 mg.), m. p. 330° (decomp.) (Found, after drying at 100°/1 mm.: C, 73·95; H, 5·25. $C_{19}H_{15}N_2Cl$ requires C, 74·4; H, 4·9%).

(*a*) Hydrogenation of the chloride (24·4 mg.) with Adams's catalyst (20 mg.) in glacial acetic acid (5 c.c.) ceased after the uptake of 2 moles of hydrogen in 70 minutes. The catalyst was filtered off after the solution had been heated to dissolve the partly precipitated hydrochloride. Isolation of the base yielded (from benzene–light petroleum) colourless needles, m. p. 197—198°, not depressed by admixture with 3 : 4 : 6 : 9-tetrahydro-7 : 8-benzindolo(2′ : 3′-1 : 2)pyridocoline.

(*b*) Hydrogenation of the chloride (21·1 mg.) with Adams's catalyst (20 mg.) in absolute alcohol (5 c.c.) containing AnalaR sodium hydroxide (4 mg.) ceased after the uptake of 1 mole of hydrogen in 10 minutes. Filtration, evaporation, and recrystallisation from aqueous alcohol yielded golden-yellow leaflets, m. p. 210—215° (decomp.) (darkening at 190°), not depressed by admixture with 3 : 4-dihydro-7 : 8-benzindolo(2′ : 3′-1 : 2)pyridocoline.

Action of Iodine on 3 : 4-*Dihydro*-7 : 8-*benzindolo*(2′ : 3′-1 : 2)*pyridocoline.*—A warm solution of the base (0·1 g.) in alcohol (10 c.c.) was treated with iodine (0·25 g.) and potassium acetate (0·5 g.) in alcohol (7·5 c.c.) as above. The product appeared to be identical with the above iodide (Found: C, 57·8; H, 4·1. Calc. for $C_{19}H_{15}N_2I$: C, 57·3; H, 3·8%). Conversion into the chloride, and repetition of the above hydrogenations gave the same results as before.

Action of Iodine on Sempervirine.—Treatment of sempervirine (14 mg.) as described in the previous paragraph, and recrystallisation of the product from alcohol, afforded golden-yellow needles, m. p. 325—328°; mixed with sempervirine hydriodide, m. p. 325—327°. Boiling with dilute sodium hydroxide solution, extraction with chloroform, drying of the extract (K_2CO_3), evaporation, and recrystallisation of the residue from aqueous alcohol afforded brownish crystals, m. p. *ca.* 256°. A dilute solution of the base in alcoholic hydrochloric acid was very pale, with a blue-violet fluorescence; addition of dilute sodium hydroxide gave a deep yellow solution without fluorescence. The identity of the base with sempervirine was confirmed by measurement of the ultra-violet absorption spectrum in alcohol.

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370. *The Ionization of Basic Triphenylmethane Dyes.*

By R. J. GOLDACRE and J. N. PHILLIPS.

The basic triphenylmethane dyes, at a given pH, reach equilibrium between kations [*e.g.*, (I)] and carbinols [*e.g.*, (II)] at rates which vary considerably for different members. Potentiometric titration being unsuitable for the determination of the basic ionization constants, a photometric method has been devised which is of general applicability to the study of kations like these, which are capable of isomerism to carbinols.

In this way, the rates of carbinol formation, and the degree of ionization *at equilibrium*, have been determined at various pH values. The ionization constants of these substances are independent of the pH values at which they were obtained and thus may be compared with those derived from a simple ionization such as that of an aromatic amine.

The significance of carbinol formation in relation to the biological action of these substances is discussed.

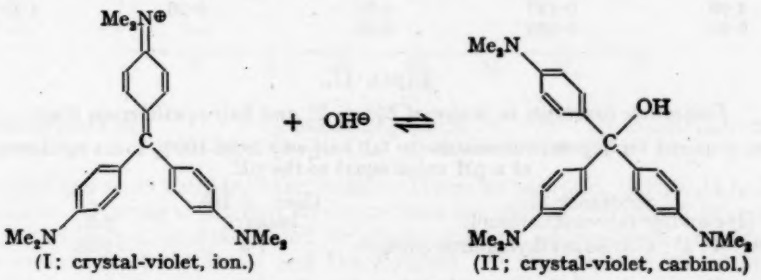
THE aminotriphenylmethane dyes are of interest from both chemical and biological angles. Though their use as dyes has diminished owing to the production of more stable substances, they occupy an important position in the theory of colour and structure; the low concentration in which some of them inhibit the growth of certain bacteria compares favourably with all other known substances (Kligler, *J. Exp. Med.*, 1918, **27**, 463; Professor S. D. Rubbo, private communication; see also Addendum, p. 1731).

It has recently been shown that, in a series of acridine bases, bacteriostatic power is proportional to the degree of ionization at pH 7 (Albert, Rubbo, Goldacre, Davey, and Stone,

Brit. J. Exp. Path., 1945, **26**, 160). A similar relation for the basic triphenylmethanes was suggested by Stearn and Stearn (*J. Bact.*, 1924, **9**, 491), who, because of the lack of ionization constants in the literature, made rough estimates of comparative basic strength on the basis of the inductive constants of substituent groups. Accurate measurements of the ionization constants of these substances are now reported, most of them for the first time.

Although acceptable measurements of several second and third ionization constants have been reported (Adams and Rosenstein, *J. Amer. Chem. Soc.*, 1914, **36**, 1452; Schwarzenbach, *Helv. Chim. Acta*, 1938, **21**, 1636), the position regarding the more interesting first constants has long been unsatisfactory. Sidgwick and Moore (*J.*, 1909, **95**, 889) and Sidgwick and Rivett (*ibid.*, p. 899) examined the effect of acid and alkali on the carbinols and salts (respectively) of brilliant-green, malachite-green, and Doebner's violet and concluded that the bases must be very strong. Rumpf (*Ann. Chim.*, 1935, [xi], **3**, 404) reported first ionization constants for *p*-aminotriphenylcarbinol (pK_a, *ca.* 4·6), Doebner's violet (*ca.* 5·8), and parafuchsin (*ca.* 7) by potentiometric titration in dilute alcohol, although this solvent complicates the picture because of ether formation (cf. Fischer, *Ber.*, 1900, **33**, 3356). Rumpf (*loc. cit.*) also roughly confirmed these figures colorimetrically. Henriquez (*Rec. Trav. chim.*, 1933, **52**, 991) obtained data from which the first ionization constant of malachite-green may be calculated.

Hantzsch and Osswald (*Ber.*, 1900, **33**, 274, 752) showed that the conductivity of the aminotriphenylmethane bases, after liberation from their salts with alkali, decreases with time. A parallel phenomenon was encountered when potentiometric titration of crystal-violet and malachite-green was attempted, the pH continuing to fall slowly after each addition of alkali. This drop in pH is brought about by the steady transformation of the dye ion (I)



(I; crystal-violet, ion.) (II; crystal-violet, carbinol.)

into the colourless carbinol (II), an isomerism caused by a hydroxyl ion attacking the central carbon atom.

An experimental method, which attempts to overcome the defects of previous methods, is described below. Water has been chosen as solvent so that the results can be used to interpret biological data. Colorimetry has been preferred to potentiometry because it permits of more accurate measurement in the dilutions (10^{-6} M.) at which it is necessary to work in order to retain the carbinol in aqueous solution. The speed at which the equilibrium (I $\leftrightarrow$ II) was attained was measured at various pH values, and the degree of ionization, at each pH value, was calculated only after equilibrium had been established. Thus the method differs from those of Hantzsch, of Sidgwick and co-workers (*loc. cit.*) and of Hochberg and LaMer (*J. Amer. Chem. Soc.*, 1941, **63**, 3110), who took no steps to control the ever-changing pH of their solutions. It is not possible to use their results to calculate equilibrium ionization constants because the speed of the reaction and the position of the equilibrium depend on the pH.

In the present method, ionization constants were calculated from the degrees of ionization of the bases at equilibrium at various pH values, by means of the law of mass action:

$$pK = pH + \log \alpha/(1 - \alpha) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where α = degree of ionization.

Typical results for malachite-green and 4-dimethylaminotriphenylcarbinol are given in Table I.

The constancy of the pK over a wide pH range indicates that the simple law of mass action, equation (1), is being obeyed, in spite of the complexity of the reaction, and of the possibility of the co-existence of various forms of ion (coloured and uncoloured) and of base as suggested by Hantzsch, by Henriquez, and by Schwarzenbach, Mohler, and Sorge (*Helv. Chim. Acta*, 1938, **21**, 1636).

TABLE I.

Effect of pH on degree of ionization.

(*a*) Malachite-green, $2{\cdot}7 \times 10^{-6}$M. at 25°.

pH.	Extinction coefficient (*E*) (red filter).	Degree of ionization (α).	log α/(1 − α).	p*K*.
4·00	0·113	1·00	—	—
6·09	0·097	0·86	0·80	6·89
6·60	0·075	0·66	0·30	6·90
6·78	0·060	0·53	0·06	6·84
6·97	0·052	0·46	−0·07	6·90
7·10	0·044	0·39	−0·20	6·90
7·42	0·026	0·23	−0·52	6·90
10·1	0·000	0·00	—	—

(*b*) 4-Dimethylaminotriphenylcarbinol, 4×10^{-5}M. at 25°.

pH.	*E* (violet filter).	α.	log α/(1 − α).	p*K*.
1·0	0·555	1·00	—	—
3·96	0·467	0·85	0·76	4·72
4·27	0·417	0·76	0·50	4·77
4·49	0·360	0·66	0·29	4·78
4·61	0·322	0·59	0·15	4·76
4·80	0·261	0·48	−0·05	4·75
4·98	0·201	0·37	−0·25	4·73
4·99	0·197	0·36	−0·26	4·73
9·20	0·000	0·00	—	—

TABLE II.

Ionization constants in water at 25° ± 2° and half-equilibrium times.

$T\frac{1}{2}$ = time required for degree of ionization to fall half-way from 100% to its equilibrium value, at a pH value equal to the p*K*.

Substance (dye and/or relevant carbinol).	Conc. × 10^6 (molar).	p*K*.	$T\frac{1}{2}$, hours.
Crystal-violet (4 : 4′ : 4″-trisdimethylaminotriphenylcarbinol)	1·8	9·36	7·5
Malachite-green (4 : 4′-bisdimethylaminotriphenylcarbinol)	2·7	6·90	2·1
Brilliant-green (4 : 4′-bisdiethylaminotriphenylcarbinol)	2·0	7·90	2·9
4-Dimethylaminotriphenylcarbinol	40·0	4·75	—
Pararosaniline (parafuchsin; 4 : 4′ : 4″-triaminotriphenylcarbinol)	3·0	{ 7·57 carbinol; >13 imine }	0·85
Doebner's violet (4 : 4′-diaminotriphenylcarbinol)	42·0	5·38	—
Michler's hydrol (4 : 4′-bisdimethylaminodiphenylcarbinol)	34·0	5·61	<0·01
Auramine (4 : 4′-bisdimethylaminodiphenylcarbinolamine)	3·9	{ 9·78 carbinol; 10·71 imine }	18·5
Fast acid green N [light green SF yellowish; Lissamine green SFS; di-sodium salt of 4 : 4′-di-(*N*-ethyl-*p*-sulphobenzylamino)triphenylcarbinol-4″-sulphonic acid]	4·5	11·0 (approx.)	—

TABLE III.

Rate of disappearance of the coloured ion of malachite-green.

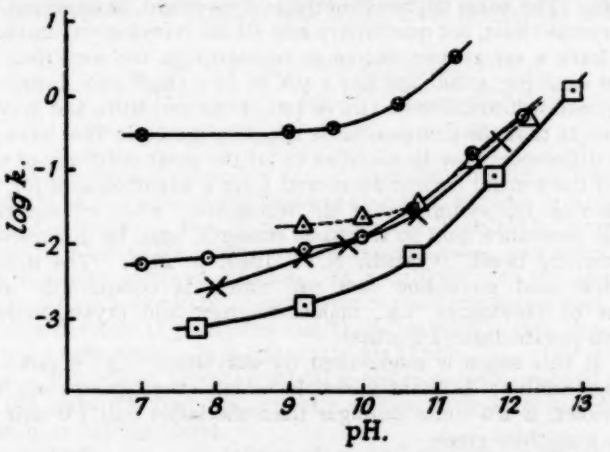
Concentration : $1{\cdot}3 \times 10^{-5}$M. at pH 7·90 (20°).

Time, mins.	Extinction coefficient (red filter).	$k \times 10^3$.	Time, mins.	Extinction coefficient (red filter).	$k \times 10^3$.
2	0·424	—	42	0·320	6·4
12	0·386	—	52	0·300	6·4
22	0·362	6·4	∞	0·100	—
32	0·341	6·0			

Ionization constants determined in this way for a number of compounds are given in Tables II and V. The attainment of equilibrium with many of the triphenylmethanes required one or two days. A rough indication of the speed is given in the fourth column (Table II), which is the

time required to proceed half-way to equilibrium at a pH equal to the pK. Velocity constants for the initial rate of disappearance of the coloured ion at various pH values are plotted in the annexed Figure. These represent apparent first-order reactions between the dye ion and the hydroxyl ion, for the latter is in large excess and is not consumed, the buffer strength being 10^{-2}M. compared with a dye concentration of about 10^{-4}M. A typical result is given in Table III. K was found to be independent of the dye concentration over a six-fold range.

Crystal-violet, malachite-green, brilliant-green, and Michler's hydrol are tertiary amines, the ions of which exist in equilibrium with the corresponding carbinol form. However, in the primary amines (pararosaniline, auramine), an additional basic form appears, the dehydrated



× *Brilliant-green* 25°. ⊙ *Malachite-green* 20°. ⊡ *Crystal-violet* 25°.
△ *Parafuchsin* 18°. ⊗ *Doebner's violet* 25°.

carbinol, variously known as anhydro-base, imine or Homolka base [*e.g.*, $(NH_2{\cdot}C_6H_4)_2C{:}C_6H_4{:}NH$ for pararosaniline]. Having a different structure from the carbinol, it should have a different pK. The equilibrium pK as determined for these primary amines is the resultant of the simultaneous ionization of the imine and the carbinol. It was possible to obtain separate ionization constants by observing at each pH the degree of ionization (*a*) at the beginning, after a primary fast equilibrium (equation 2), and (*b*) after the system had finally reached equilibrium due to a subsequent slow reaction (equation 3).

$$\text{Fast reaction: } X'{=}NH_2^{\oplus} + OH^{\ominus} \longrightarrow X{=}NH \text{ (imine)} + H_2O \quad . \; . \quad (2)$$

$$\text{Slow reaction: } X'{=}NH + H_2O \longrightarrow OH{-}X{-}NH_2 \text{ (carbinol)} \quad . \; . \; . \quad (3)$$

Reaction (2), which involves only ions, is almost instantaneous. It yields a pK for the imine (constant, *e.g.*, for auramine within $\pm 0{\cdot}1$ pK unit over a range of 20—83% ionization) which is higher than that found when the system has finally reached equilibrium (Table IV).

TABLE IV.

Instantaneous and equilibrium ionization constants of triphenylmethane dyes having a primary amino-group.

	Auramine.	Pararosaniline.
Instantaneous pK of imine	10·71	about 13—14
Equilibrium pK	9·84	7·57
Carbinol pK (calc.)	9·78	7·57
[Carbinol]/[imine] at equilibrium	8·5	10^6

Auramine, though not a triphenylmethane dye, was included because of its close relation to pararosaniline. Only a rough estimate for the imine pK of the latter was possible because it was necessary to work at pH 13. This is above the range of accurate measurement by the glass electrode, and the pH was calculated from the concentration of potassium hydroxide in the solution. In aqueous solution, the imine changed much more rapidly into the carbinol than was the case with auramine. The amount of imine present was determined by taking advantage of the fact that it is yellow and soluble in ether, whereas the salt and the carbinol do not dissolve in ether. In wet ether the change to the carbinol (by hydration) is slow. The pH giving half

the maximum depth of colour in the ether, when the solution was shaken with a given ratio of ether immediately after mixing the buffer and the dye, was taken as the pK of the imine (Table IV).

In auramine the imine and carbinol are colourless, but the slow change of the former into the latter was followed in the ultra-violet region at 3650 A. where the difference in light absorption was great. A velocity constant at pH 10 of approximately 10^{-2} was obtained. The change is ascribed to the transformation of imine (strong base) into carbinol (weaker base), both eventually reaching equilibrium with the coloured ion.

Results.—These will be discussed under five headings.

(i) *Basic strength.* The basic triphenylmethane dyes might be expected to be strong bases, for some, such as crystal-violet, are quaternary and all are (vinylogous) amidines and guanidines and hence should have a far greater degree of resonance in the ions than exists in the non-ionized bases. For example, guanidine has a pK of 13·6 (Hall and Sprinkle, *J. Amer. Chem. Soc.*, 1932, **54**, 3469) and benzamidine of 11·6 (0·1M., cf. Albert, Mills, and Royer, *J.*, 1948, 1452). It is seen from Table II that the common basic triphenylmethane dyes have comparatively low pK values. These differences may be ascribed to (*a*) the great tendency of the hydroxyl ion to become attached to the central carbon atom and form a carbinol, and (*b*), in some cases, the effect of substitution on the symmetry of the resonance; when substitution diminishes the symmetry, the ionic resonance, and so the basic strength, may be diminished (Pauling, " The Nature of the Chemical Bond," Cornell, N.Y., 1940, p. 215). The difference in strength between benzamidine and guanidine (2·0 pK units) is comparable with that between corresponding pairs of vinylogues, *e.g.*, malachite-green and crystal-violet (2·5 units), and Doebner's violet and parafuchsin (2·2 units).

Basic strength in this series is augmented by alkylation, *e.g.*, crystal-violet is 1·8 units stronger than pararosaniline; brilliant-green, in which ethyl groups are substituted in the parent Doebner's violet, is 2·5 units stronger than the latter and 1·0 unit stronger than the methyl-substituted malachite-green.

The pK of Michler's hydrol is surprisingly low, when compared with that of malachite-green, in which a phenyl group replaces the central hydrogen atom of the hydrol. The phenyl group is usually base-weakening, through its electron-attracting effect, and this is one of the rare examples in which it brings about the opposite result.

In Fast acid green N the three negatively-charged sulpho-groups repel hydroxyl ions from the dye ion, and this effect augments the usual inductive effect, so that the basic strength is increased by three pK units above that of the parent, brilliant-green.

The value of the pK found for malachite-green (6·90 at 25°) agrees well with a value of 6·96 at 20°, calculated from data reported by Henriquez (*loc. cit.*).

(ii) *Velocity constants.* In the Figure (which shows the dependence of the initial velocity constant on pH) the slope of the curves above pH 10 is approximately 45°, indicating that the speed of the reaction is proportional to the hydroxyl-ion concentration. This is consistent with the view that the dominating reaction is the combination of the dye cation with the hydroxyl ion, until the rate of formation of the carbinol equals its rate of dissociation.

The curves become more nearly horizontal at about pH 10, below which the rate of carbinol-formation is faster than that corresponding to the concentration of hydroxyl ions present. A similar effect was observed by Schwarzenbach, Mohler, and Sorge (*loc. cit.*) at pH 1 for phenolindophenol, and was ascribed to a back reaction, becoming great at and below a pH equal to the pK, which was 0·95. However, the deviation from linearity occurs at the pK only for crystal-violet, and at a much higher pH for the other substances. The reason for the deviation is obscure. It is unlikely to be caused by a precipitation of the carbinol, unseen because of the low concentration of dye used (about 1—10 mg./l.) because the constancy of the pK with change in pH (Table I), and of the velocity constant with change in concentration, indicates that precipitation does not occur.

(iii) *Imines.* From the instantaneous pK (due to the imine) and the equilibrium pK, the carbinol pK of auramine and rosaniline can be calculated (see Table IV) as follows:

$$K_{\text{equilib.}} = \frac{[H^+]\{[B_{\text{carbinol}}] + [B_{\text{imine}}]\}}{[BH^+]}$$

$$= \frac{[H^+][B_{\text{carbinol}}]}{[BH^+]} + \frac{[H^+][B_{\text{imine}}]}{[BH^+]}$$

$$= K_{\text{carbinol}} + K_{\text{imine}} \quad \ldots\ldots\ldots\ldots \quad (4)$$

where $K_{equilib.}$ = equilibrium K, $B_{carbinol}$ = carbinol base, B_{imine} = imine base, BH^+ = ion, K_{imine} = imine K, and $K_{carbinol}$ = carbinol K.

That there should be an equilibrium between the imine base and carbinol base is reasonable, as both are in equilibrium with the ion (equation 5). The statement that the change of imine to carbinol is " irreversible " (Sidgwick, " Organic Chemistry of Nitrogen," Oxford, 1937, 91) is probably intended to convey that the equilibrium is displaced largely to one side.

$$[B_{imine}] + [H_2O] \rightleftharpoons [B_{carbinol}] \quad . \ . \ . \ . \ . \ . \ . \ . \quad (5)$$

Since the concentration of water is constant, the ratio of imine to carbinol is constant. This ratio can be calculated from the $K_{carbinol}$ and K_{imine} from the law of mass action for each reaction :

$$pH - pK_{imine} = \log ([B_{imine}]/[BH^+])$$

$$pH - pK_{carbinol} = \log ([B_{carbinol}]/[BH^+])$$

Therefore,

$$\log([B_{carbinol}]/[B_{imine}] = pK_{imine} - pK_{carbinol} \quad . \ . \ . \ . \ . \ . \quad (6)$$

Thus, of the total non-ionized auramine base in equilibrium with its ion, 92% is in the form of the carbinol and 8% in the form of the imine (Table IV), whereas in rosaniline only one part in a million is in the form of the imine. Thus, the " unstable intermediate carbinol," $Me_2N{\cdot}C_6H_4{\cdot}C(OH)(NH_2){\cdot}C_6H_4{\cdot}NMe_2$ postulated by Hantzsch (*loc. cit.*) is really the main form in which non-ionized auramine exists in solution. It is unlikely that the assignment of the pK's to the imine and the carbinol should be reversed, for experiment shows that in those compounds which can form only a carbinol (*e.g.*, crystal-violet) the reaction is very slow (Table II), whereas the reaction assigned to the imine pK is instantaneous (Table IV). For example, it was found experimentally, for a given dye, that the initial extinction coefficients of a series of solutions differing only in pH were different for primary amines such as auramine, but identical for tertiary amines such as crystal-violet.

The ratio, $[B_{carbinol}] : [B_{imine}]$, may be regarded as a hydration constant (equation 5), and in the two compounds examined the hydration (addition of one molecule of water across the double bond) goes almost to completion.

(iv) *The interpretation of the* p*K*. The pK values reported here have been calculated from the observed degrees of ionization. In these calculations the quantity measured has always been the amount of coloured ion (at equilibrium) under given conditions compared with the total amount of coloured ion under those less alkaline conditions which ensure the presence of the maximum amount of it.

No regard has been paid to the various forms of colourless bases that may exist (cf. Schwarzenbach; Henriquez, *locc. cit.*), apart from the imine and carbinol, or to the colourless (hydrated) ions which appear to exist in the so-called " white salts " (Hantzsch and Osswald, *loc. cit.*). There is an equilibrium between all these forms in solution; the pK values reported are based on the observed degrees of ionization, which will be n% of the maximum for the coloured ion when it is n% of the maximum for any colourless ion, provided that equilibrium has been reached. For any one substance, the pK value for each type of monoacidic cation may be different, but the degree of ionization at a given pH, expressed as a fraction of the total amount capable of existing in the one particular ionic form at equilibrium, is the same for each. The concentration of colourless ions seems to be very small. No evidence has been found for the existence of the " ammonium bases " postulated by Hantzsch.

The pK values reported above facilitate calculations of changes in the concentration of the coloured ion with changing pH. Such calculations, which were not available to Stearn and Stearn (*loc. cit.*), will be of value in testing their hypothesis that the coloured cations were the species responsible for anti-bacterial activity in this series. The predicted order of basic strength (brilliant-green > crystal-violet > fuchsin) * derived by these authors from a consideration of inductive constants, is not supported by the values in Table II. It is to be expected, from considerations of the distribution of lipophobic and lipophilic groups in the various ions, that differences in adsorbability on the bacteria will also contribute to differences in biological activity.

The method used here for the triphenylmethanes is equally applicable to other series where equilibrium involving carbinols occurs. Table V gives the results of applying it to some quaternary acridines.

* Fuchsin is a mixture of parafuchsin and a homologue which is *C*-methylated *ortho* to the central carbon atom.

TABLE V.

Ionization constants of some quaternary acridines in water at 25° ± 1°.

Substance.	pK_a.	Conc. × 10^{-5} (molar).
10-Methylacridinium bromide	9·75	3·0
5-Amino-10-methylacridinium bromide	11·01	2·0
2-Amino-10-methylacridinium bromide	11·85	2·0

(v) *Interpretations of miscellaneous results obtained with basic triphenylmethane dyes.* Hantzsch and Osswald (*loc. cit.*) found that when one equivalent of potassium hydroxide was added to an M/250-crystal-violet solution, the colour of the last portion of the crystal-violet persisted with great tenacity no matter how long the two substances were left in contact; he ascribed this to the accidental entry of CO_2. However, calculation from the pK reveals that the reaction could never go to completion under these conditions; the pH would have fallen to 10·7 (corresponding to 5% ionization) when 5% of the alkali was left. A further fall in pH would cause increased ionization of crystal-violet (pK 9·36). This alone would suffice to explain the persistent colour.

Sidgwick and Rivett (*loc. cit.*) found a pK_a of 5·8 for Doebner's violet, when hydrochloric acid was added to a solution of the carbinol, and of 10·6 when alkali was added to the salt. Evidently not sufficient time had elapsed to allow equilibrium to be reached, but the former figure may be compared with the constant pK (Table II) of 5·38 from measurements made over the whole of the pH scale.

It has also been stated that brilliant-green has $K = 0{\cdot}00531$ (Sidgwick and Moore, *loc. cit.*), which would make it stronger than ammonia, but the present results show that it is weaker.

The Figure indicates that, even in neutral solutions of the dyes, slow reaction with hydroxyl ions takes place. For example, at pH 7·3, the degree of ionization of malachite-green slowly falls from 100% at zero time to 28·5% at infinite time. The time factor must be borne in mind when using the pK_a to calculate the degree of ionization in a solution of known pH. If stock solutions are required to be kept for some time, the slow precipitation of carbinol can be avoided by the addition of hydrochloric acid to bring the solution to about pH 4.

The dyeing of wool by crystal-violet was investigated by Elöd (*Trans. Faraday Soc.*, 1933, **29**, 327) over a pH range of 0—12. The amount of dye taken up increased with rising pH to a maximum at pH 8·5, above which it decreased sharply. The author ascribed this to an "enlargement of the particles" of the dye, but it is evident that, as the solution proceeds to equilibrium above this pH, the concentration of coloured ion will fall, especially if carbinol is precipitated.

When a slight excess of alkali was added to solutions of various members of this series, the carbinols which were precipitated were usually strongly dyed with the ion from which they were produced. This suggests a strong tendency to complex formation between the ion and carbinol which is also exhibited at the oil–water interface. When pure carbon tetrachloride or chloroform was shaken with a neutral aqueous solution of crystal-violet (or other member of the series), the colour remained in the water, but after several hours it appeared in the organic solvent. The time required for this to happen was shorter at higher pH values. If the carbinol was first added to the chloroform (by extracting some of the dye solution to which excess of alkali had been added), the chloroform immediately extracted the colour from the aqueous phase. A similar result was obtained when a trace of oleic acid was added to the solvent. Evidently an oil-soluble complex of ion and carbinol was formed.

Heymann and Joffe (*Trans. Faraday Soc.*, 1942, **38**, 408) drew attention to an unusual property of methyl-violet and malachite-green. Although many substances which are active at the air–water interface are comparably active at the oil–water interface, crystal-violet and brilliant-green exerted a much greater effect at the oil–water interface. Schulman and Cockbain (*Trans. Faraday Soc.*, 1940, **36**, 651) have shown that, when a complex can be formed between an oil-soluble and a water-soluble substance, an exceptionally great lowering of the oil–water interfacial tension occurs when the substances are present in the appropriate phases. A likely interpretation of the results of Heymann and Joffe is that a small quantity of carbinol formed by reaction with hydroxyl ions enters the oil, and it is immediately fixed at the interface by complex formation with coloured ions in the water. This could not happen at the air–water interface, so that the tension lowering there is slight.

Deviation from Beer's law in the cations of the compounds studied was found to be appreciable down to concentrations of the order of 10^{-5}M. In general, the non-alkylated

amines deviated 10% at about one-tenth the concentration of those having tertiary amino-groups. The deviation suggests that a tendency to micelle formation in the ions is facilitated by primary amino-groups, probably through hydrogen bonding (cf. Rabinowitch and Epstein, *J. Amer. Chem. Soc.*, 1941, **63**, 69; Michaelis and Granick, *ibid.*, 1945, **67**, 1212).

Experimental.

Care was taken to free the distilled water from dust by filtration, since dust was observed to adsorb the dye readily and to remove an appreciable proportion of it at the high dilution used. Equal amounts of a solution of the dye salt were added to a series of 0·01M-borate, -phosphate, or -acetate buffers of various pH values; potassium hydroxide was used for high pH values. The pH was measured with a glass electrode before and after photometry, and the depth of colour estimated on a Hilger absorptiometer, using the filter which was found by experiment to give a maximum change in extinction coefficient with change in pH. If a turbidity was found in the upper pH range (by observing any scattering at right angles to a beam of light), a lower concentration of dye was used until no precipitation occurred. Readings were taken at intervals until equilibrium was established.

The ionization constants were determined by finding the degree of ionization at various pH values by optical means. The degree of ionization of the triphenylmethane dyes was taken as proportional to the extinction coefficient of the solution, corrected for deviation from Beer's law where necessary. The extinction coefficients corresponding to 0% and 100% ionization were taken as those which were constant over a range of several pH units at the upper and lower end, respectively, of the range. In some cases a small correction for the second ionization constant, obtained from the literature or determined experimentally, was applied in the calculation of the extinction value for 100% ionization. At low degrees of ionization the correction was usually negligible.

Reaction velocities at various pH values were calculated from the rate of disappearance of the coloured ion. Readings were taken every few minutes in a room in which the temperature was approximately constant.

With the quaternary acridines (Table V), there was only a small difference between the light-absorption of the ion and that of the carbinol, whereas there was a large difference in fluorescence. The degree of ionization was measured on the Klett photoelectric fluorimeter.

Some potentiometric titrations were attempted in 50% acetone, which, unlike alcohol, does not react chemically with the carbinols. At a glass electrode, 10-methylacridinium bromide gave a pK of 8·71 (cf. 9·75 in water, Table V), equilibrium being reached almost instantly after each addition of alkali. Equilibration was much slower with crystal-violet: the pH of a half-neutralized M./200 solution in 50% aqueous acetone (kept stoppered in the dark) fell steadily from an initial value of 12·2 (glass electrode, uncorrected) to 9·0 in 5 hours, 8·7 in 2 days, and 8·2 in 30 days (cf. pK 9·36 in water, Table II). Thus, acetone has lowered these two equilibrium values by approximately 1 pK unit, and it was found to depress the pK of 5-aminoacridine, which cannot form a carbinol, by the same amount.

Materials.—Crystal-violet was purified as the carbinol, m. p. 219° (corr.), by the method of Kovache (*Ann. Chim.*, 1918, [ix], **10**, 247). Malachite-green, brilliant-green, and parafuchsin were purified by the partition method of Lewis, Magel, and Lipkin (*J. Amer. Chem. Soc.*, 1942, **64**, 1782). 4-Dimethylaminotriphenylcarbinol, m. p. 92—93°, and 4 : 4′-diaminotriphenylcarbinol, m. p. 173—175° (decomp.), were prepared and purified according to Baeyer and Villiger (*Ber.*, 1904, **37**, 2857). Michler's hydrol, m. p. 102—103°, was prepared by the method of Nathanson and Miller (*Ber.*, 1889, **22**, 1879). Auramine base, m. p. 136°, was liberated from a pure specimen of auramine and recrystallized from benzene. Fast acid green N (required for approximate results only) was used in the form of Lissamine green SFS (I.C.I.). The preparation of the acridinium compounds is described in Albert, Rubbo, Goldacre, Davey, and Stone (*loc. cit.*).

Addendum (by S. D. Rubbo; June 10th, 1949).

Bacteriostatic Action of Aminotriphenylmethanes.

Highest dilutions of triphenylmethanes completely preventing visible growth in 48 hours at 37° (pH 7·2—7·4).

Medium: A, plain broth; B, 10% serum broth.

		Organisms.				
-triphenylcarbinol.	Medium.	*Cl. welchii.* 1 in.	*Strep. pyogenes.* 1 in.	*Staph. aureus.* 1 in.	*B. coli.* 1 in.	*Proteus.* 1 in.
4-Dimethylamino-	A	10,000	*	*	*	*
	B	*	*	*	*	*
4 : 4′-Diamino- (Doebner's violet)	A	10,000	80,000	20,000	*	*
	B	*	20,000	20,000	*	*
4 : 4′-Bisdimethylamino- (malachite-green)	A	1,280,000	320,000	80,000	*	*
	B	320,000	80,000	40,000	*	*
4 : 4′ : 4″-Triamino- (parafuchsin; pararosaniline)	A	160,000	160,000	160,000	*	*
	B	10,000	80,000	160,000	5,000	*
4 : 4′-Bisdiethylamino- (brilliant-green)	A	640,000	1,280,000	1,280,000	*	*
	B	160,000	320,000	40,000	*	*
4 : 4′ : 4″-Trisdimethylamino- (crystal-violet)	A	160,000	320,000	2,560,000	10,000	20,000
	B	80,000	80,000	640,000	5,000	20,000

* Growth not prevented by 1 : 5,000 dilution.

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UNIVERSITY OF SYDNEY. [*Received, November 12th*, 1948.]

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371. *Synthetic Antimalarials. Part XLII. The Preparation of Guanylureas and Biurets corresponding to "Paludrine" and related Diguanides.*

By (the late) F. H. S. CURD, D. G. DAVEY, and (MISS) D. N. RICHARDSON.

Deamination of N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide to give N-p-*chlorophenyl*-N′-iso*propylguanylurea* is effected by prolonged standing in acid solution or by treatment with excess of nitrous acid. The constitution of this guanylurea was proved by its synthesis from *p*-chlorophenyl *iso*cyanate and *iso*propylguanidine. In common with a number of related *N*-*p*-chlorophenyl-*N*′-alkylguanyl- and -*N*′*N*′-dialkylguanyl-ureas, also synthesised, it showed activity against the erythrocytic, but not against the exo-erythrocytic, forms of *P. gallinaceum*, whereas the isomeric N-p-*chlorophenylguanyl*-N′-iso*propylurea* was inactive.

A number of related 1-*p*-chlorophenyl-5-alkyl- and -5 : 5-dialkyl-biurets has also been prepared, but none of these compounds exhibited any antimalarial activity.

IT has been shown by Spinks and Tottey (*Ann. Trop. Med. Parasit.*, 1945, **39**, 220) (see also Spinks, *ibid.*, 1946, **40**, 101) that the antimalarial "Paludrine" (I; R = H, R′ = Pr^i) is quantitatively hydrolysed to *p*-chloroaniline by heating with 0·25N-hydrochloric acid in an autoclave at 20—25 lb./sq. in. steam-pressure.

More recently, the observation has been made in these laboratories by Mr. R. S. Neal that when N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide was kept in 2N-hydrochloric acid, gradual deposition of the hydrochloride of another compound occurred. This latter salt gave analytical figures which suggested that it was one or other of the corresponding guanylureas (II) and (III; R = Cl, R′ = H, R″ = Pr^i). It was therefore decided to undertake the unambiguous synthesis of these compounds, not only in an attempt to establish the constitution of the transformation product, but also in order to examine them for antimalarial activity since it seemed possible that they might be implicated in the *in vivo* degradation of "Paludrine" through deamination. It may be noted that the corresponding guanylthioureas were without antimalarial activity (Parts XXIX and XXX, *J.*, 1948, 1636, 1645), but it was thought that this might be due to internal-salt formation which would be less likely in the case of the guanylureas.

Unsuccessful attempts to prepare arylguanylureas by the condensation of aryl *iso*cyanates with guanidine have been recorded in the literature by Slotta, Tschesche, and Dressler (*Ber.*, 1930, **63**, 208); *e.g.*, phenyl *iso*cyanate afforded only the bis-condensation product, *NN*′-bisphenylcarbamylguanidine. No reference could be found to the reaction of aryl *iso*cyanates with substituted guanidines, but in an earlier paper (Part XXIX, *loc. cit.*) it was shown that aryl *iso*thiocyanates in general condense with mono- and di-alkylguanidines to give *N*-aryl-*N*′-alkyl-(or -*N*′*N*′-dialkyl-)guanylthioureas, although in certain cases substances arising from the condensation of 2 molecules of *iso*thiocyanate with one molecule of guanidine were formed, either as the main product or as a by-product. It has now been found that aryl *iso*cyanates interact under similar conditions, in acetone solution, with mono- or di-alkylguanidines to give *N*-aryl-*N*′-alkyl- (or -*N*′*N*′-dialkyl-)guanylureas. Thus *p*-chlorophenyl *iso*cyanate with methylguanidine gave N-p-*chlorophenyl*-N′-*methylguanylurea* (III; R = Cl, R′ = H, R″ = Me), and with ethylguanidine afforded the corresponding *ethyl* compound (III; R = Cl, R′ = H, R″ = Et). Similarly, phenyl *iso*cyanate condensed with *NN*-dimethylguanidine to give N-*phenyl*-N′-(NN-*dimethylguanyl*)*urea* (III; R = H, R′ = R″ = Me). However, when *p*-chlorophenyl *iso*cyanate was condensed with *iso*propyl- or *n*-butyl-guanidine the respective products, N-p-*chlorophenyl*-N′-iso*propylguanylurea* and N-p-*chlorophenyl*-N′-n-*butylguanylurea*, were accompanied by small amounts of less soluble, higher-melting, materials, but the nature of these was not investigated.

N-*p*-Chlorophenyl-*N*′-*iso*propylguanylurea prepared by this method was found to be identical with the hydrolysis product of (I; R = H, R′ = Pr^i), formed, as mentioned above, by prolonged standing in acid solution.

An alternative method for the preparation of this type of compound was opened up by the observation of our colleague, Dr. J. A. Hendry, that N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide with excess of nitrous acid in aqueous solution afforded *N*-*p*-chlorophenyl-*N*′-*iso*propylguanylurea identical with material made by the method mentioned above. Similarly, N^1-*p*-chlorophenyl-

N^5N^5-dimethyldiguanide on treatment with nitrous acid gave N-p-*chlorophenyl*-N′-(NN-*dimethylguanyl*)*urea* (III; R = Cl, R′ = R″ = Me), indistinguishable from the product of interaction of *p*-chlorophenyl *iso*cyanate and *NN*-dimethylguanidine, and the method was then used to prepare N-p-*chlorophenyl*-N′-(N-*methyl*-N-iso*propylguanyl*)*urea* (III; R = Cl, R′ = Me, R″ = Pr^i) and N-p-*chlorophenyl*-N′-(NN-*diethylguanyl*)*urea* (III; R = Cl, R′ = R″ = Et).

The results of antimalarial tests, against *P. gallinaceum* in chicks, carried out with the guanylureas, of type (III) are shown in the table below. It will be seen that, whilst they all show some activity against the blood forms, the variations in activity in no way parallel those observed with the corresponding diguanides (cf. Part X, *J.*, 1946, 729). Further, the guanylureas, unlike the diguanides, exhibit no prophylactic activity even at maximum tolerated doses, and there can therefore be no question of the antimalarial activity of the diguanides being due to *in vivo* deamination to the corresponding guanylureas.

The only compound of the *N*-arylguanyl-*N′*-alkylurea series prepared was N-p-*chlorophenyl-guanyl*-N′-iso*propylurea* (II), which resulted from the interaction of *iso*propyl *iso*cyanate and *p*-chlorophenylguanidine, but this compound was devoid of antimalarial activity (see Table) and the type was not further investigated.

Antimalarial Activities.

The compounds were tested for antimalarial activity against the blood forms of *P. gallinaceum* in chicks using the method previously described (Davey, *Ann. Trop. Med. Parasit.*, 1946, **40**, 52). The results given below are expressed in the same way as in previous papers in this series.

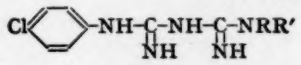
Ref. no.	Compound.	Dose, mg./kg.	Activity.
6354	*N-p*-Chlorophenyl-*N′*-methylguanylurea	80	++
		40	+
6615	*N-p*-Chlorophenyl-*N′*-ethylguanylurea	80	++
		40	+
		20	—
6045	*N-p*-Chlorophenyl-*N′-iso*propylguanylurea	80	+ to ++
		40	—
5964	*N-p*-Chlorophenyl-N′-*n*-butylguanylurea	160	++
		80	+
		40	—
5940	*N*-Phenyl-*N′*-(*NN*-dimethylguanyl)urea	80	—
5963	*N-p*-Chlorophenyl-*N′*-(*NN*-dimethylguanyl)urea	80	++
		40	+ to ++
		20	—
6661	*N-p*-Chlorophenyl-*N′*-(*N*-methyl-*N-iso*propylguanyl)urea	80	++
		40	+
		20	±
6814	*N-p*-Chlorophenyl-*N′*-(*NN*-diethylguanyl)urea	80	++
		40	++
6111	*N-p*-Chlorophenylguanyl-*N′-iso*propylurea	80	—
5965	1-Phenyl-5-*p*-chlorophenylbiuret	160	—
6031	1-*p*-Chlorophenyl-5-methylbiuret	80	—
6088	1-*p*-Chlorophenyl-5-ethylbiuret	40	—
6106	1-*p*-Chlorophenyl-4-methyl-5-*iso*propyl-4-*iso*biuret	80	—
6114	1-*p*-Chlorophenyl-5-*iso*propylbiuret	80	— (toxic)
		40	—
6178	1-*p*-Chlorophenyl-5-*n*-butylbiuret	40	—
6011	1-*p*-Chlorophenyl-4 : 5 : 5-trimethyl-4-*iso*biuret	80	—
6105	1-*p*-Chlorophenyl-4 : 5-dimethyl-5-*iso*propyl-4-*iso*biuret	80	—
6110	1-*p*-Chlorophenyl-5-methyl-5-*iso*propylbiuret	80	—
6078	1-*p*-Chlorophenyl-4-methyl-5 : 5-*cyclo*pentamethylene-4-*iso*biuret	Not tested	
6263	1-*p*-Chlorophenyl-5 : 5-*cyclo*pentamethylenebiuret	80	—

All the compounds were tested also for prophylactic activity against *P. gallinaceum* by the method described by one of us (Davey, *Ann. Trop. Med. Parasit.*, 1946, **40**, 453), in the majority of cases at the maximum tolerated dose (the highest dose quoted above) but at half this dose in the case of 5964, 5965, and 6114, and at 120 mg./kg. in the case of 6661. All were inactive. 6078 was tested at 160 mg./kg.

Despite the inactivity of (II) it seemed desirable to investigate some biurets analogous to the active diguanides (I; R = alkyl, R′ = H or alkyl), since it appeared conceivable that *in-vivo* deamination of the latter might proceed further than the guanylurea stages.

Several methods of preparing biuret derivatives have been described in the literature, and some have been reinvestigated with a view to the preparation of 1-*p*-chlorophenyl-5-alkyl- and 5 : 5-dialkyl-biurets (IV; R = alkyl, R′ = H or alkyl).

Kuhn and Henschel (*Ber.*, 1888, **21**, 504) have stated that, whereas the condensation of phenyl *iso*cyanate with *NN'*-diphenylurea gave rise to 1 : 3 : 5-triphenylbiuret as the sole product, with phenylurea there was formed a small quantity of a higher-melting by-product in addition to 1 : 5-diphenylbiuret. Similarly, it has now been found that condensation of phenyl *iso*cyanate with *p*-chlorophenylurea, and of *p*-chlorophenyl *iso*cyanate with phenylurea, gave rise to mixtures which could not be separated. Moreover, Biltz and Jeltsch (*Ber.*, 1923, **56**, 1915) treated phenyl *iso*cyanate with methylurea at 120—130° in a closed vessel and obtained a product, m. p. 172—173°, which they claimed to be 1-phenyl-5-methylbiuret. Gatewood (*J. Amer. Chem. Soc.*, 1925, **47**, 407) repeated this reaction at 80—90° and obtained a different product, m. p. 132—133°, which was shown to be authentic 1-phenyl-5-methylbiuret by its independent synthesis from *N*-carbethoxy-*N'*-phenylurea (ethyl *N*$^{\omega}$-phenyl allophanate) and methylamine. In a later paper, Biltz and Beck (*Ber.*, 1925, **58**, 2187) acknowledged the difference in the products and repeated the reaction to give 1-phenyl-5-methylbiuret, m. p. 133°. With an excess of phenyl *iso*cyanate, however, another compound, m. p. 183°, was also formed which was found to be identical with the product obtained by Gatewood (*loc. cit.*) by the action of methyl sulphate on 1-phenylbiuret and considered to be 1-phenyl-3-methylbiuret. Although no attempt has been made to confirm this work it was taken to indicate the possibility of the formation of more than one product and the method, therefore, appeared unsuitable for our purpose.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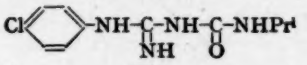
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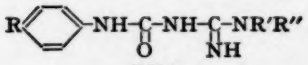
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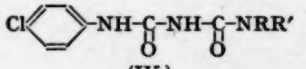
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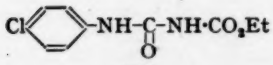
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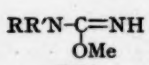
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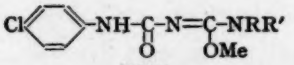
(VII.)

Another method for the preparation of biurets which, although not always successful, has been used by several previous workers (cf., *e.g.*, Biltz and Jeltsch, *loc. cit.*; Wertheim, *J. Amer. Chem. Soc.*, 1931, **53**, 200; Chabrier de la Saulnière, *Ann. Chim.*, 1942, **17**, 353; Gatewood, *loc. cit.*) is the reaction of allophanic esters with amines. By use of this method 1-p-*chlorophenyl*-5-*methyl*- (IV; R = H, R' = Me) and 1-p-*chlorophenyl*-5-*ethyl*-*biuret* (IV; R = H, R' = Et) were prepared by the action of methylamine and ethylamine respectively on N-*carbethoxy*-N'-p-*chlorophenylurea* (V), but it failed when applied to *iso*propylamine, *n*-butylamine, or dimethylamine, *p*-chlorophenylurea being the only isolable product.

The *N*-carbethoxy-*N'*-*p*-chlorophenylurea (V) required for this work was prepared by the action of ethyl carbonate on *p*-chlorophenylurea in alcoholic sodium ethoxide solution. This method was taken from D.R.-P. 427,417, which *inter alia* described the preparation of *N*-carbethoxy-*N'*-phenylurea from phenylurea and ethyl carbonate under these conditions. Other methods described in the literature for the preparation of *N*-carbethoxy-*N'*-phenylurea included the condensation of phenyl *iso*cyanate with urethane (Dains, Greider, and Kidwell, *J. Amer. Chem. Soc.*, 1919, **41**, 1004; cf. Folin, *Amer. Chem. J.*, 1897, **19**, 323) and the reaction of *N*-carbethoxyurea with aniline at 120—125° (Dains and Wertheim, *J. Amer. Chem. Soc.*, 1920, **42**, 2303), but these methods appeared too liable to be complicated by side-reactions and were therefore not seriously considered for the preparation of (V). The work of Biltz and Jeltsch (*loc. cit.*) who prepared *N*-carbethoxy-*N'*-methylurea from methylurea and ethyl chloroformate suggested a similar reaction with *p*-chlorophenylurea but an attempt to effect this failed.

Attention was then directed to the work of McKee (*Amer. Chem. J.*, 1901, **26**, 209) who prepared a number of *iso*biurets by condensation of phenyl *iso*cyanate with *O*-alkyl*iso*ureas and *N*-aryl-substituted derivatives thereof, and converted them into the corresponding biurets by spontaneous decomposition of the hydrochlorides in a vacuum (loss of alkyl chloride) or by boiling hydrochloric acid. We have verified the applicability of the method to the preparation of 1 : 5-diarylbiurets in the following way. *N*-Phenyl-*O*-methyl*iso*urea (McKee, *loc. cit.*) and the corresponding p-*chlorophenyl* derivative (prepared by the action of dry hydrogen chloride on *p*-chlorophenylcyanamide in methanol, followed by decomposition of the resulting hydrochloride with alkali) were condensed with *p*-chlorophenyl *iso*cyanate and phenyl *iso*cyanate respectively

to give 1-*phenyl*-5-p-*chlorophenyl*-4-*methyl*-4-iso*biuret* and 1-*phenyl*-5-p-*chlorophenyl*-2-*methyl*-2-iso*biuret* (VII; R = H, R′ = Ph), both of which in boiling 2N-hydrochloric acid afforded 1-*phenyl*-5-p-*chlorophenylbiuret* (IV; R = H, R′ = Ph). 1-p-*Chlorophenylbiuret* (IV; R = R′ = H) was prepared by condensing *p*-chlorophenyl *iso*cyanate with *O*-methyl*iso*urea to give 1-p-*chlorophenyl*-4-*methyl*-4-iso*biuret* (VII; R = R′ = H) which was boiled with hydrochloric acid, and the method was then extended, in the first instance, to the synthesis of a number of 1-*p*-chlorophenyl-5 : 5-dialkylbiurets. The preparation of various *O*-methyl- (and *O*-ethyl)-*NN*-dialkyl*iso*ureas from the corresponding dialkylcyanamides has been described by McKee (*ibid.*, 1909, **42**, 1), either through the hydrochlorides which were obtained by the action of dry hydrogen chloride in methanol, or preferably by the action of methanolic sodium methoxide (alcoholic sodium ethoxide for the *O*-ethyl compounds). The former method was used to prepare *ONN*-trimethyl*iso*urea (cf. McKee) and the latter for ON-*dimethyl*-N-iso*propyl*iso*urea* (VI; R = Me, R′ = Pr^i) and O-*methyl*-NN-cyclo*pentamethylene*iso*urea* (VI; R and R′ = $[CH_2]_5$). These *O*-methyl-*NN*-dialkyl*iso*ureas condensed with *p*-chlorophenyl *iso*cyanate in ether to give 1-*p*-chlorophenyl-4-methyl-5 : 5-dialkyl-4-*iso*biurets of type (VII) which were decomposed by boiling dilute hydrochloric acid to give the required 1-*p*-chlorophenyl-5 : 5-dialkylbiurets (IV; R and R′ = alkyl). Thus *p*-chlorophenyl *iso*cyanate and *ONN*-trimethyl*iso*urea gave 1-p-*chlorophenyl*-5 : 5-*dimethylbiuret* (IV; R = R′ = Me) by way of 1-p-*chlorophenyl*-4 : 5 : 5-*trimethyl*-4-iso*biuret* (VII; R = R′ = Me), and the corresponding 5-*methyl*-5-iso*propyl* (IV; R = Me, R′ = Pr^i) and 5 : 5-cyclo*pentamethylene* (IV; R and R′ = $[CH_2]_5$) compounds were prepared analogously.

For the preparation of 1-*p*-chlorophenyl-5-monoalkylbiurets by a similar method, *O*-alkyl-*N*-monoalkyl*iso*ureas were required. It has been found that the *O*-methyl*iso*ureas can be prepared by passing dry hydrogen chloride into a solution of the monoalkylcyanamide (prepared *in situ* from the amine and cyanogen bromide) and excess methanol in ether, followed by liberation of the base with sodium hydroxide. In this way *ON*-dimethyl*iso*urea (VI; R = H, R′ = Me) (not analysed) was made in small yield, and converted, by the action of *p*-chlorophenyl *iso*cyanate, into 1-p-*chlorophenyl*-4 : 5-*dimethyl*-4-iso*biuret* (VII; R = H, R′ = Me) which in boiling 2N-hydrochloric acid afforded 1-*p*-chlorophenyl-5-methylbiuret, identical with the product obtained from *N*-carbethoxy-*N′*-*p*-chlorophenylurea and methylamine (see above). This synthesis of the same biuret by two different methods was held to substantiate its structure and therefore that of the analogous compounds prepared by either method. The exact biuret analogue (IV; R = H, R′ = Pr^i) of " Paludrine " was then prepared by converting *iso*propyl-cyanamide into O-*methyl*-N-iso*propyl*iso*urea* (VI; R = H, R′ = Pr^i), condensing this with *p*-chlorophenyl *iso*cyanate, and decomposing the resulting 1-p-*chlorophenyl*-4-*methyl*-5-iso*propyl*-4-iso*biuret* (VII; R = H, R′ = Pr^i) with acid. 1-*p*-Chlorophenyl-5-*n*-butylbiuret (IV; R = H, R′ = Bu^n) was prepared analogously from *n*-butylcyanamide through (VI; R = H, R′ = Bu^n) and (VII; R = H, R′ = Bu^n).

Experimental.

Hydrolysis of " Paludrine " with Cold Hydrochloric Acid (Experiment by Mr. R. S. Neal).—N^1-*p*-Chlorophenyl-N^5-*iso*propyldiguanide (20 g.) was dissolved in 2N-hydrochloric acid (125 c.c.) and the solution set aside for 1 year. A crystalline solid was gradually deposited which was eventually collected and crystallised from water to give colourless flat prisms, m. p. 126—127°, which showed no depression when mixed with *N*-*p*-chlorophenyl-*N′*-*iso*propylguanylurea hydrochloride (see below). When this hydrochloride was dissolved in water and the solution made alkaline with ammonia, the corresponding base was obtained. It was collected, washed with water, dried, and crystallised from benzene; m. p. 133°, either alone or in admixture with *N*-*p*-chlorophenyl-*N′*-*iso*propylguanylurea made by the methods described below (Found: C, 51·6; H, 5·7; N, 22·0; Cl, 13·9, 14·2. $C_{11}H_{15}ON_4Cl$ requires C, 51·9; H, 5·9; N, 22·0; Cl, 13·9%).

N-p-*Chlorophenyl*-N′-*methylguanylurea* (III; R = Cl, R′ = H, R″ = Me).—Sodium (1·9 g.) was dissolved in acetone (100 c.c.) (previously dried over potassium carbonate and distilled over phosphoric oxide), and methylguanidine sulphate (11·5 g.) added. After the mixture had been stirred for 1 hour, phenyl *iso*cyanate (9·6 g.) in acetone (50 c.c.) was added, and the mixture stirred at 35—40° for 1½ hours and then poured into water. When kept, the precipitated oil gradually solidified and was collected, washed with water, and dried. Crystallisation from toluene gave N-p-*chlorophenyl*-N′-*methylguanylurea* as colourless prisms (8·5 g.), m. p. 130—132° (Found: C, 48·0; H, 5·1; N, 24·1. $C_9H_{11}ON_4Cl$ requires C, 47·7; H, 4·9; N, 24·7%) (6354).

N-p-*Chlorophenyl*-N′-*ethylguanylurea* (III; R = Cl, R′ = H, R″ = Et).—Prepared similarly from *p*-chlorophenyl *iso*cyanate and ethylguanidine sulphate, the *product* crystallised from benzene as colourless prisms, m. p. 142—144° (Found: C, 49·6; H, 5·4; N, 23·8. $C_{10}H_{13}ON_4Cl$ requires C, 49·9; H, 5·4; N, 23·3%) (6615).

N-*Phenyl*-N′-(NN-*dimethylguanyl*)*urea* (III; R = H, R′ = R″ = Me).—Prepared in an analogous manner from phenyl *iso*cyanate and *NN*-dimethylguanidine sulphate, this *compound* crystallised from

benzene as colourless elongated flat prisms, m. p. 130—132° (Found : C, 58·2; H, 6·9; N, 27·0. $C_{10}H_{14}ON_4$ requires C, 58·25; H, 6·8; N, 27·2%) (5940).

N-p-*Chlorophenyl*-N′-iso*propylguanylurea* (III; R = Cl, R′ = H, R″ = Pr^i).—(*a*) To a solution of sodium (1·9 g.) in dry acetone (100 c.c.) *iso*propylguanidine sulphate (14 g.) was added, and the mixture stirred for 1½ hours. A solution of *p*-chlorophenyl *iso*cyanate (9·6 g.) in acetone (50 c.c.) was then added, and the mixture stirred at 30—35° for 2 hours and poured into water. The sticky solid precipitated was collected and dissolved in hot 50% aqueous alcohol, which when cooled and set aside deposited a substance, m. p. 208—210°. This was removed by filtration and discarded. The mother-liquors were diluted with water to precipitate N-p-*chlorophenyl*-N′-iso*propylguanylurea* which was collected, dried, and crystallised from benzene; it formed colourless flat prisms, m. p. 131—133° (Found : C, 52·1; H, 5·7; N, 21·6. $C_{11}H_{15}ON_4Cl$ requires C, 51·9; H, 5·9; N, 22·0%) (6045).

(*b*) N^1-*p*-Chlorophenyl-N^5-*iso*propyldiguanide hydrochloride (2·53 g.) was dissolved in N-hydrochloric acid (100 c.c.), and sodium nitrite (5 g.) added gradually at room temperature. A solid soon separated and was collected and crystallised from water to give N-p-*chlorophenyl*-N′-iso*propylguanylurea hydrochloride* as clusters of colourless prisms, m. p. 126—127° (Found : C, 42·8; H, 5·8; N, 17·8. $C_{11}H_{15}ON_4Cl,HCl,H_2O$ requires C, 42·7; H, 5·8; N, 18·1%). Addition of ammonia to a solution of this hydrochloride in water precipitated the base which crystallised from benzene; m. p. 131—133°, undepressed in admixture with material made by method (*a*) (Found : C, 51·7; H, 5·8; N, 22·4%).

N-p-*Chlorophenyl*-N′-n-*butylguanylurea* (III; R = Cl, R′ = H, R″ = Bu^n).—Prepared from *p*-chlorophenyl *iso*cyanate and *n*-butylguanidine sulphate as described under (*a*) above, the crude product was obtained as an oil on pouring the reaction mixture into water. It was separated by decantation and dissolved in hot alcohol. A small amount of a high-melting insoluble by-product was removed by filtration at this stage and the alcoholic filtrate poured into water. The precipitated oil soon solidified and was then collected, dried, and crystallised from benzene–light petroleum (b. p. 60—80°) to give N-p-*chlorophenyl*-N′-n-*butylguanylurea* as colourless prisms, m. p. 108—110° (Found : C, 53·5; H, 6·5; N, 20·6; Cl, 13·4. $C_{12}H_{17}ON_4Cl$ requires C, 53·6; H, 6·3; N, 20·8; Cl, 13·2%) (5964).

N-p-*Chlorophenyl*-N′-(NN-*dimethylguanyl*)*urea* (III; R = Cl, R′ = R″ = Me).—(*a*) Prepared from *p*-chlorophenyl *iso*cyanate and *NN*-dimethylguanidine sulphate as described above, the *product* crystallised from benzene as colourless prisms, m. p. 151—153° (Found : C, 49·8; H, 5·1; N, 23·1; Cl, 14·6. $C_{10}H_{13}ON_4Cl$ requires C, 49·9; H, 5·4; N, 23·3; Cl, 14·8%) (5963).

(*b*) N^1-*p*-Chlorophenyl-N^5N^5-dimethyldiguanide (8·28 g.) was dissolved in a mixture of water (125 c.c.) and 10N-hydrochloric acid (46 c.c.). Sodium nitrite (18·2 g.) was gradually added and the mixture stirred for 1½ hours. The precipitated solid was filtered off and stirred with dilute sodium hydroxide solution. The resulting base was collected, washed with water, and dried to give the same material as in (*a*); m. p. and mixed m. p. 151—152°.

N-p-*Chlorophenyl*-N′-(N-*methyl*-N-iso*propylguanyl*)*urea* (III; R = Cl, R′ = Me, R″ = Pr^i).—N^1-*p*-Chlorophenyl-N^5-methyl-N^5-*iso*propyldiguanide (32·1 g.) was dissolved in a mixture of 10N-hydrochloric acid (186 c.c.) and water (500 c.c.), and sodium nitrite (64·2 g.) added with stirring. The mixture was stirred for 1½ hours whereupon an oil separated on the surface. The oil was separated, stirred with aqueous sodium hydroxide, and extracted with ether. Evaporation of the dried (K_2CO_3) extract gave N-p-*chlorophenyl*-N′-(N-*methyl*-N-iso*propylguanyl*)*urea* which crystallised from benzene–light petroleum (b. p. 60—80°) as colourless flat prisms (10·5 g.), m. p. 132—133° (Found : C, 53·5; H, 6·3; N, 21·2. $C_{12}H_{17}ON_4Cl$ requires C, 53·6; H, 6·3; N, 20·8%) (6661).

N-p-*Chlorophenyl*-N′-(NN-*diethylguanyl*)*urea* (III; R = Cl, R′ = R″ = Et), prepared similarly from N^1-*p*-chlorophenyl-N^5 : N^5-diethyldiguanide, crystallised from light petroleum (b. p. 100—120°) as colourless prisms, m. p. 116—117° (Found : C, 53·5; H, 5·9; N, 20·7. $C_{12}H_{17}ON_4Cl$ requires C, 53·6; H, 6·3; N, 20·8%) (6814).

N-p-*Chlorophenylguanyl*-N′-iso*propylurea* (II).—*p*-Chlorophenylguanidine (8·48 g.) was dissolved in benzene (50 c.c.), and *iso*propyl *iso*cyanate (4·25 g.) (Hofmann, *Ber.*, 1882, **15**, 756) added. Heat was evolved and a solid separated. After the mixture had been kept overnight, the solid was collected and crystallised from chlorobenzene to give the *product* as colourless laminæ (11 g.), m. p. 172—174° (Found : C, 52·0; H, 5·8; N, 22·6. $C_{11}H_{15}ON_4Cl$ requires C, 51·9; H, 5·9; N, 22·0%) (6111). The hydrochloride had m. p. 160—162°.

N-*Carbethoxy*-N′-p-*chlorophenylurea* (V).—*p*-Chlorophenylurea (17 g.) and ethyl carbonate (12·5 g.) were added to a solution of sodium (2·3 g.) in dry alcohol (60 c.c.), and the mixture boiled under reflux for 1 hour. The precipitated solid was collected, suspended in water, and acidified with acetic acid. The resulting product was extracted with chloroform, and the extract dried and evaporated. Crystallisation of the residue from methanol gave N-*carbethoxy*-N′-p-*chlorophenylurea* as long colourless prisms (11·9 g.), m. p. 162° (Found : C, 49·3; H, 4·7; N, 11·5. $C_{10}H_{11}O_3N_2Cl$ requires C, 49·5; H, 4·5; N, 11·5%).

Condensation of N-*Carbethoxy*-N′-p-*chlorophenylurea with Methylamine.*—The above compound (4 g.) and 21% aqueous methylamine (50 c.c.) were heated together at 100° in a closed vessel for 1 hour. The crystalline product which separated on cooling was collected, washed with water, and dried. Crystallisation from methanol gave 1-p-*chlorophenyl*-5-*methylbiuret* as colourless thin prisms (2 g.), m. p. 182° (Found : C, 47·8; H, 4·3; N, 18·1. $C_9H_{10}O_2N_3Cl$ requires C, 47·5; H, 4·4; N, 18·5%) (6031). See also p. 1738.

Condensation of N-*Carbethoxy*-N′-p-*chlorophenylurea with Ethylamine.*— N-Carbethoxy-N′-*p*-chlorophenylurea (5 g.) and 33% aqueous ethylamine (50 c.c.) reacted as in the preceding experiment to give 1-p-*chlorophenyl*-5-*ethylbiuret* which crystallised from methanol as colourless prisms (4·1 g.), m. p. 180—182° (Found : C, 49·2; H, 4·8; N, 17·4. $C_{10}H_{13}O_2N_3Cl$ requires C, 48·7; H, 5·0; N, 17·4%) (6088).

Condensation of N-*Carbethoxy*-N′-p-*chlorophenylurea with* iso*Propylamine.*—N′-Carbethoxy-N-*p*-chlorophenylurea (4 g.), *iso*propylamine (18 c.c.), and water (22 c.c.) were heated at 100° in a closed vessel for 1 hour. After cooling, the reaction mixture was diluted with water, and the product collected. Crystallised from methanol it had m. p. 206—208°, either alone or in admixture with *p*-chlorophenylurea (Young and Dunstan, *J.*, 1908, **93**, 1058). Similar results were obtained using *n*-butylamine and dimethylamine.

N-p-*Chlorophenyl*-O-*methyl*iso*urea* (VI; R = H, R′ = *p*-C_6H_4Cl).—*p*-Chlorophenylcyanamide (15 g.) was dissolved in dry methanol (100 c.c.), and dry hydrogen chloride passed in until the gain in weight was 7 g. The solution was set aside for 2 days and then poured into excess of potassium hydroxide solution. The precipitated solid was extracted with ether and filtered from a little insoluble material (*p*-chlorophenylurea), and the solution dried (Na_2SO_4) and evaporated. Crystallisation of the residue from light petroleum (b. p. 60—80°) gave N-p-*chlorophenyl*-O-*methyl*iso*urea* as colourless laminæ, m. p. 62—63° (Found: C, 52·5; H, 4·6; N, 14·9. $C_8H_9ON_2Cl$ requires C, 52·0; H, 4·9; N, 15·2%).

1-*Phenyl*-5-p-*chlorophenyl*-2-*methyl*-2-iso*biuret* (VII; R = H, R′ = Ph).—*p*-Chlorophenyl *iso*cyanate (7·7 g.) in dry ether (20 c.c.) was added to a solution of *N*-phenyl-*O*-methyl*iso*urea (8·25 g.) (McKee, *Amer. Chem. J.*, 1901, **26**, 209) in the same solvent (20 c.c.). Heat was evolved. After 2 hours, light petroleum (b. p. 40—60°) was added to precipitate the *product* which was collected, washed, and crystallised from light petroleum (b. p. 80—100°), to give colourless long thin prisms, m. p. 106—108° (Found: C, 59·4; H, 4·6; N, 13·9. $C_{15}H_{14}O_2N_2Cl$ requires C, 59·3; H, 4·6; N, 13·8%).

1-*Phenyl*-5-p-*chlorophenyl*-4-*methyl*-4-iso*biuret*.—Prepared similarly from phenyl *iso*cyanate and *N*-*p*-chlorophenyl-*O*-methyl*iso*urea, this *compound* crystallised from light petroleum (b. p. 80—100°) as colourless long prisms, m. p. 92—94° (Found: C, 59·3; H, 4·7; N, 13·8; Cl, 12·1. $C_{15}H_{14}O_2N_2Cl$ requires C, 59·3; H, 4·6; N, 13·8; Cl, 11·7%).

1-*Phenyl*-5-p-*chlorophenyl*biuret (IV; R = H, R′ = Ph).—(*a*) 1-Phenyl-5-*p*-chlorophenyl-4-methyl-4-*iso*biuret (5 g.) and 2N-hydrochloric acid (50 c.c.) were boiled under reflux for 1½ hours. Methyl chloride was evolved. After the mixture had cooled, the solid reaction product was collected, dried, and washed with ether. Crystallisation from alcohol then gave 1-*phenyl*-5-p-*chlorophenyl*biuret as colourless long flat needles, m. p. 216—218° (Found: C, 58·5; H, 4·1; N, 14·5. $C_{14}H_{12}O_2N_2Cl$ requires C, 58·0; H, 4·1; N, 14·5%) (5965).

(*b*) 1-Phenyl-5-*p*-chlorophenyl-2-methyl-2-*iso*biuret (5 g.) was boiled under reflux with 2N-hydrochloric acid (50 c.c.) to give the same compound as in (*a*); m. p. and mixed m. p. 216—218°.

1-p-*Chlorophenyl*-4-*methyl*-4-iso*biuret* (VII; R = R′ = H).—*p*-Chlorophenyl *iso*cyanate (4·5 g.) in ether (25 c.c.) was added to *O*-methyl*iso*urea (2·4 g.) (McKee, *Amer. Chem. J.*, 1901, **26**, 247) in ether (25 c.c.). After a few minutes, the *product* was precipitated with light petroleum (b. p. 40—60°). Next day it was collected and crystallised from light petroleum (b. p. 100—120°); colourless elongated prisms (5·6 g.), m. p. 120° (Found: C, 47·8; H, 4·1; N, 18·0. $C_9H_{10}O_2N_2Cl$ requires C, 47·5; H, 4·4; N, 18·5%) (6179).

1-p-*Chlorophenyl*biuret (IV; R = R′ = H).—The preceding compound (2·5 g.) and 2N-hydrochloric acid (25 c.c.) were boiled under reflux for 1 hour, the mixture cooled, and the product collected and washed with water. Crystallisation from aqueous methanol gave 1-p-*chlorophenyl*biuret as colourless thick prisms, m. p. 182—184° (Found: C, 45·3; H, 3·9. $C_9H_9O_2N_2Cl$ requires C, 45·0; H, 3·7%).

ONN-*Trimethyl*iso*urea* (VI; R = R′ = Me).—Dimethylcyanamide (14·6 g.) was dissolved in dry methanol (100 c.c.), and dry hydrogen chloride passed in until the gain in weight was 8 g. After 8 days the solution was evaporated under diminished pressure at <35°. The white solid residue was kept overnight in a desiccator containing solid potassium hydroxide and concentrated sulphuric acid. It was then dissolved in water (20 c.c.), ether (100 c.c.) added, and the mixture cooled in solid carbon dioxide. Solid sodium hydroxide (60 g.) was carefully added, the ether decanted, and the residue washed twice with ether (100 c.c.). Evaporation of the combined, dried (Na_2SO_4), ethereal extracts and distillation of the residue gave *ONN*-trimethyl*iso*urea (7·35 g.), b. p. 80°/85 mm.

ON-*Dimethyl*-N-iso*propyl*iso*urea* (VI; R = Me, R′ = Pr^i).—Methyl*iso*propylcyanamide (12·1 g.) (Ainley, Curd, and Rose, this vol., p. 98) was added to a solution of sodium (3·2 g.) in methanol (50 c.c.), and the mixture stirred at 50—55° for 2 hours. After cooling, the solution was diluted with water, and hydrochloric acid added to render the solution just acid to Congo-red. It was then shaken with ether to remove any unchanged methyl*iso*propylcyanamide, made alkaline with sodium hydroxide, and again extracted with ether. Evaporation of the dried (Na_2SO_4) ether extract and distillation of the residue gave the *product* as a colourless oil (10·4 g.), b. p. 70°/12 mm. (Found: C, 55·2; H, 10·7. $C_6H_{14}ON_2$ requires C, 55·4; H, 10·8%).

O-*Methyl*-NN-cyclo*pentamethylene*iso*urea* (VI; R and R′ = <[CH_2]$_5$), prepared analogously from *cyclo*pentamethylenecyanamide, formed a colourless oil, b. p. 102—104°/14 mm. (Found: C, 58·5; H, 9·5; N, 19·7. $C_7H_{14}ON_2$ requires C, 59·1; H, 9·9; N, 19·7%).

1-p-*Chlorophenyl*-4 : 5 : 5-*trimethyl*-4-iso*biuret* (VII; R = R′ = Me).—A solution of *ONN*-trimethyl-*iso*urea (7·5 g.) in dry ether (30 c.c.) was added to one of *p*-chlorophenyl *iso*cyanate (10 g.) in dry ether (30 c.c.). Heat was evolved, and the *product* separated. After a few minutes it was collected, dried, and crystallised from benzene; colourless rods (10·25 g.), m. p. 129° (Found: C, 51·7; H, 5·5; N, 16·1. $C_{11}H_{14}O_2N_2Cl$ requires C, 51·7; H, 5·5; N, 16·4%) (6011).

1-p-*Chlorophenyl*-4 : 5-*dimethyl*-5-iso*propyl*-4-iso*biuret* (VII; R = Me, R′ = Pr^i).—Similarly prepared by use of *ON*-dimethyl-*N*-iso*propyl*iso*urea* and precipitated from the reaction mixture by the addition of light petroleum (b. p. 40—60°), this *compound* crystallised from light petroleum (b. p. 80—100°) as colourless elongated prisms, m. p. 104° (Found: C, 55·4; H, 6·4; N, 14·6. $C_{13}H_{18}O_2N_2Cl$ requires C, 55·0; H, 6·3; N, 14·8%) (6105).

1-p-*Chlorophenyl*-4-*methyl*-5 : 5-cyclo*pentamethylene*-4-iso*biuret* (VII; R and R′ = <[CH_2]$_5$).—Prepared in a corresponding manner from *O*-methyl-*NN*-*cyclo*pentamethylene*iso*urea, the *product* crystallised from light petroleum (b. p. 100—120°) as colourless thick prisms, m. p. 126° (Found: C, 57·2; H, 6·2; N, 14·2. $C_{14}H_{18}O_2N_2Cl$ requires C, 56·9; H, 6·1; N, 14·2%).

1-p-*Chlorophenyl*-5 : 5-*dimethyl*biuret (IV; R = R′ = Me).—1-*p*-Chlorophenyl-4 : 5 : 5-trimethyl-4-*iso*biuret (5 g.) was dissolved in 2N-hydrochloric acid (50 c.c.), and the solution boiled under reflux for 1 hour. Methyl chloride was evolved. The product which separated was collected, after cooling, and purified by crystallisation from methanol; colourless thick plates, m. p. 184—186° (Found: C, 51·1; H, 5·0. $C_{10}H_{12}O_2N_2Cl$ requires C, 49·7; H, 5·0%).

1-p-*Chlorophenyl*-5-*methyl*-5-iso*propyl*biuret (IV; R = Me, R′ = Pr^i).—Prepared similarly from the corresponding *O*-methyl*iso*biuret (VII; R = Me, R′ = Pr^i), this *biuret* crystallised from light petroleum

(b. p. 80—100°) as colourless, long, thin prisms, m. p. 142—144° (Found: C, 52·2; H, 5·8; N, 14·8. $C_{12}H_{16}O_2N_2Cl$, $0·5H_2O$ requires C, 51·7; H, 6·1; N, 15·1%) (6110).

1-p-*Chlorophenyl*-5 : 5-cyclo*pentamethylene*biuret (IV; R and R′ = $<[CH_2]_5$), prepared similarly from (VII; R and R′ = $<[CH_2]_5$), crystallised from acetone as colourless long prisms, m. p. 194—196° (Found: C, 55·9; H, 5·7; N, 14·9. $C_{12}H_{16}O_2N_2Cl$ requires C, 55·4; H, 5·7; N, 14·9%).

ON-*Dimethylisourea* (VI; R = H, R′ = Me).—Gaseous methylamine (35 g.) was absorbed in dry ether (200 c.c.), and cyanogen bromide (68 g.) added slowly to the stirred solution cooled to −5° to −10°. The temperature was kept at or below −5°. When the addition was complete, the mixture was stirred for ½ hour, and the mixture filtered to remove methylamine hydrobromide. To the filtrate dry methanol (300 c.c.) was added, and dry hydrogen chloride passed in until the gain in weight was *ca.* 40 g. After 4 days the solution was evaporated under reduced pressure, and the residue dissolved in a small quantity of water. Ether was added, followed by sodium hydroxide to make the mixture strongly alkaline. The ethereal layer was separated, and the aqueous layer re-extracted twice with ether. Evaporation of the dried (Na_2SO_4) ethereal extracts gave *ON*-dimethyl*iso*urea, b. p. 68°/16 mm., in very small yield.

O-*Methyl*-N-iso*propyl*iso*urea* (VI; R = H, R′ = Pr^i), similarly prepared from *iso*propylamine, formed a colourless oil (yield, 22·7%), b. p. 77°/12 mm. (Found: C, 51·7; H, 10·3; N, 23·7. $C_5H_{12}ON_2$ requires C, 51·7; H, 10·3; N, 24·1%).

O-*Methyl*-N-n-*butyl*iso*urea* (VI; R = H, R′ = Bu^n), prepared analogously from *n*-butylamine, was obtained as a colourless oil (yield, 55%), b. p. 90°/10 mm. (Found: C, 55·7; H, 11·1; N, 21·5. $C_6H_{14}ON_2$ requires C, 55·4; H, 10·8; N, 21·5%).

1-p-*Chlorophenyl*-4 : 5-*dimethyl*-4-iso*biuret* (VII; R = H, R′ = Me).—*ON*-Dimethyl*iso*urea (0·8 g.) and *p*-chlorophenyl *iso*cyanate (1·3 g.) were allowed to react in ether (15 c.c.) and, after a few minutes, light petroleum (b. p. 40—60°) was added to precipitate the product. This was collected and crystallised from light petroleum (b. p. 100—120°) to give 1-p-*chlorophenyl*-4 : 5-*dimethyl*-4-iso*biuret* (1·45 g.), m. p. 135—137° (Found: C, 49·6, 49·7; H, 5·0, 5·0; N, 17·8. $C_{10}H_{12}O_2N_2Cl$ requires C, 49·7; H, 5·0; N, 17·4%).

1-p-*Chlorophenyl*-4-*methyl*-5-iso*propyl*-4-iso*biuret* (VII; R = H, R′ = Pr^i), prepared similarly from *O*-methyl-*N*-*iso*propyl*iso*urea, crystallised from light petroleum (b. p. 60—80°) as colourless flat needles, m. p. 82—84° (Found: C, 53·5; H, 6·0; N, 15·6. $C_{12}H_{16}O_2N_2Cl$ requires C, 53·4; H, 5·9; N, 15·6%) (6106).

1-p-*Chlorophenyl*-5-*methylbiuret* (IV; R = H, R′ = Me).—1-*p*-Chlorophenyl-4 : 5-dimethyl-4-*iso*biuret (1·2 g.) and 2N-hydrochloric acid (12 c.c.) were boiled under reflux for 1 hour, and the resulting precipitate filtered off, after cooling, washed with water, dried, and crystallised from methanol to give the product (0·8 g.), m. p. 182—184°, undepressed by admixture with material made by condensation of *N*-carbethoxy-*N*′-*p*-chlorophenylurea and methylamine (see above).

1-p-*Chlorophenyl*-5-iso*propylbiuret* (IV; R = H, R′ = Pr^i).—Similarly prepared by treatment of 1-*p*-chlorophenyl-4-methyl-5-*iso*propyl-4-*iso*biuret (5 g.) with boiling 2N-hydrochloric acid (50 c.c). for 1½ hours, this *compound* crystallised from aqueous methanol as colourless flat needles (yield, 3·9 g.), m. p. 184° (Found: C, 51·6; H, 5·4; N, 15·9. $C_{11}H_{14}O_2N_2Cl$ requires C, 51·7; H, 5·5; N, 16·4%) (6114).

1-p-*Chlorophenyl*-5-n-*butylbiuret* (IV; R = H, R′ = Bu^n).—*O*-Methyl-*N*-*n*-butyl*iso*urea (8·4 g.) in ether (20 c.c.) was treated with a solution of *p*-chlorophenyl *iso*cyanate (9 g.) in ether (50 c.c.). After the spontaneous reaction had subsided, the bulk of the solvent was evaporated, and light petroleum (b. p. 40—60°) added. After 48 hours a small amount of solid which had separated was removed by filtration. The filtrate was evaporated to leave 1-*p*-chlorophenyl-4-methyl-5-*n*-butyl-4-*iso*biuret which solidified slowly when kept but could not be recrystallised. The crude material (10 g.) was accordingly boiled with 2N-hydrochloric acid (100 c.c.) for 1 hour under reflux. The oily layer which formed solidified gradually and, after cooling, the solid was collected, washed with water, and dried. Crystallisation from aqueous methanol afforded 1-p-*chlorophenyl*-5-n-*butylbiuret* as colourless thick prisms, m. p. 141—143° (Found: C, 53·2; H, 5·9; N, 15·5. $C_{12}H_{16}O_2N_2Cl$ requires C, 53·4; H, 5·9; N, 15·6%) (6178).

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372. *Synthetic Antimalarials. Part XLIII. Some Dithiobiurets and 1 : 2 : 4-Triazoles related to "Paludrine."*

By (the late) F. H. S. CURD, D. G. DAVEY, (Miss) D. N. RICHARDSON, and (in part) R. DE B. ASHWORTH.

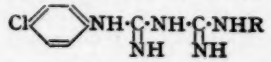
1-*p*-Chlorophenyl-5-*iso*propyldithiobiuret and a number of related substances of type (II) have been prepared by reaction of the corresponding 1-aryl-4-ethyl-5-alkyl-4-*iso*dithiobiurets (III) with sodium hydrogen sulphide, and examined for antimalarial activity. Unlike the analogous diguanides described in Part X (Curd and Rose, *J.*, 1946, 729), none exhibited any activity.

Using the 5-*iso*propyl compound as an example, it has been shown that the primary ethylation product of the 1-aryl-5-alkyldithiobiurets, like that of the 1-aryldithiobiurets (Johnson, *Amer. Chem. J.*, 1903, **30**, 167) is the 2-*S*-ethyl derivative (VI). Similarly, the 4-*S*-ethyl compounds (III) from which the normal dithiobiurets of type (II) were derived, and which were prepared by condensation of aryl *iso*thiocyanates with *S*-ethyl-*N*-alkyl*iso*thioureas, were further ethylated to give 2 : 4-di-*S*-ethyl derivatives (VII). By the action of hydrazine on this type of compound a number of 3-arylamino-5-alkylamino-1 : 2 : 4-triazoles (VIII) were prepared, but despite their obvious structural similarity to the diguanides (I) they were without antimalarial activity. This is discussed.

1-*p*-Chlorophenyl-5-*iso*propyldithiobiuret and its 2- and 4-*S*-ethyl derivatives were all converted into N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide by reaction with ammonia and mercuric oxide. The suggestion is made that such reactions proceed *via* intermediate carbodi-imide stages and must accordingly be stepwise.

The investigation also included some miscellaneous work on monothiobiurets, such as the preparation of 1-p-*chlorophenyl*-5-iso*propyl*-4-*thiobiuret* (X; R = Pr^i), and the corresponding 5-*ethyl* compound. Neither showed any antimalarial activity.

THE preceding paper described the synthesis, and examination for antimalarial activity, of a number of guanylurea and biuret analogues of the active N^1-aryl-N^5-alkyldiguanides such as "Paludrine" (I; R = Pr^i). In the present investigation this exploration of compounds related to the diguanides has been extended, in the first place to the analogous dithiobiurets (II). When our investigation was complete it came to our notice that a number of 1-aryldithiobiurets had been examined under the American wartime antimalarial programme (Wiselogle, "Survey of Antimalarial Drugs," 1941—1945, p. 656) without the disclosure of any marked antimalarial activity. More recently, the preparation of the exact dithiobiuret analogue (II; R = Cl, R′ = H, R″ = Pr^i) of "Paludrine" has been reported (Fullhart, *Iowa State College J. Sci.*, 1947, **22**, 27) but no detailed account has yet appeared and no results of antimalarial tests have so far been published. Dr. Fullhart has, however, kindly sent us details of his work. From this it appears that *iso*propyl *iso*thiocyanate was condensed with *N*-*p*-chloro-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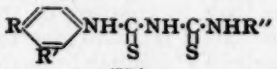
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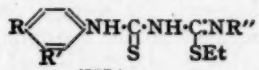

(III.)

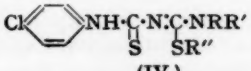
phenyl-*S*-methyl*iso*thiourea in aqueous alcoholic solution to give 1-*p*-chlorophenyl-2-methyl-5-*iso*propyl-2-*iso*dithiobiuret which, without purification, was thiohydrolysed with sodium hydrogen sulphide to give (II; R = Cl, R′ = H, R″ = Pr^i). One of our first approaches to this compound was by the same method, but since, in one experiment, we failed to effect the condensation of *iso*propyl *iso*thiocyanate with *N*-*p*-chlorophenyl-*S*-methyl*iso*thiourea in ethereal solution, we turned our attention to the condensation of *p*-chlorophenyl *iso*thiocyanate with *S*-ethyl-*N*-*iso*propyl*iso*thiourea. This was successfully effected in ether, but more conveniently in aqueous-alcoholic solution, to give 1-p-*chlorophenyl*-4-*ethyl*-5-iso*propyl*-4-iso*dithiobiuret* (III; R = Cl, R′ = H, R″ = Pr^i), which was thiohydrolysed by boiling with alcoholic sodium hydrogen sulphide, saturated with hydrogen sulphide, to give 1-*p*-chlorophenyl-5-*iso*propyldithiobiuret.

Using similar procedures, the following dithiobiurets of type (II) were made: 1-p-*chlorophenyl*-5-*methyl*-, -5-*ethyl*-, -5-n-*propyl*-, -5-n-*butyl*-, 1-m-*chlorophenyl*-5-iso*propyl*-, 1-p-*bromophenyl*-5-iso*propyl*-, 1-p-*iodophenyl*-5-iso*propyl*-, and 1-3′ : 4′-*dichlorophenyl*-5-iso*propyl*-.

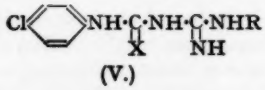
That the synthesis had indeed taken the expected course was proved by treating not only 1-*p*-chlorophenyl-5-*iso*propyldithiobiuret, but also the 4-*S*-ethyl compound (III; R = Cl, R′ = H, R″ = Pr^i) from which it was derived, with alcoholic ammonia in presence of mercuric oxide to give, in both cases, N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide. In a similar manner, 1-*p*-chlorophenyl-5-methyldithiobiuret afforded N^1-*p*-chlorophenyl-N^5-methyldiguanide (I; R = Me).

In the conversion of 1-*p*-chlorophenyl-4-ethyl-5-*iso*propyl-4-*iso*dithiobiuret into N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide it seemed possible that the desulphurising agent was unnecessary for the replacement of the *S*-ethyl group by NH_2. This was supported by the observation that 1-*p*-chlorophenyl-4-methyl-4-*iso*dithiobiuret (IV; R = R′ = H, R″ = Me) reacted with *iso*propylamine, without the intervention of any desulphurising agent, to give *N*-*p*-chlorophenyl-*N*′-*iso*propylguanylthiourea (V; X = S, R = Pr^i) identical with material prepared by condensation of *p*-chlorophenyl *iso*thiocyanate with *iso*propylguanidine (see Part XXIX, *J.*, 1948, 1636). Analogously (IV; R = R′ = H, R″ = Me) shaken with aqueous alcoholic methylamine gave N-p-*chlorophenyl*-N′-*methylguanylthiourea* (V; R = Me), and reacted with methanolic ammonia to give *N*-*p*-chlorophenyl-*N*′-guanylthiourea (Part XXXVII, this vol., p. 475).

Evidence has been adduced to support the belief that the conversion of *N*-aryl-*N*′-alkylguanylthioureas and *N*-arylguanyl-*N*′-alkylthioureas and their respective *S*-alkyl derivatives into N^1-aryl-N^5-alkyldiguanides, described in Parts XXIX and XXX (*J.*, 1948, 1636, 1645), proceeded *via* a carbodi-imide stage, and if the same mechanism operated in the analogous conversion of dithiobiurets of types (II) and (III) into diguanides the reaction must necessarily have been stepwise. Some support for this mechanism is provided by the Indian patent 37,045 which claims the conversion of 1-substituted dithiobiurets into dicyandiamides by reaction with ammonia in presence of a desulphurising agent, and by our failure to convert into diguanides *iso*dithiobiurets of the type (IV; R and R′ = alkyl) in which the necessary hydrogen atoms for carbodi-imide formation are not available. The compounds studied were 1-p-*chlorophenyl*-5 : 5-*dimethyl*-4-*ethyl*-4-iso*dithiobiuret* (IV; R = R′ = Me, R″ = Et) and 1-p-*chlorophenyl*-5-*methyl*-4-*ethyl*-5-iso*propyl*-4-iso*dithiobiuret* (IV; R = Me, R′ = Pr^i, R″ = Et) which were prepared by the action of *p*-chlorophenyl *iso*thiocyanate on *NN*-dimethyl-*S*-ethyl*iso*thiourea



(IV.)



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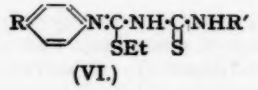


(VI.)

and *N*-methyl-*S*-ethyl-*N*-*iso*propyl*iso*thiourea respectively, with a view to the preparation of 1-*p*-chlorophenyl-5 : 5-dimethyl- and 1-*p*-chlorophenyl-5-methyl-5-*iso*propyl-dithiobiuret. However, attempts to effect the thiohydrolysis of (IV; R = R′ = Me, R″ = Et) and (IV; R = Me, R′ = Pr^i, R″ = Et) were unsuccessful, apparently because of breakdown of the molecule, since neither starting material nor dithiobiuret could be isolated.

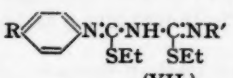
This was unfortunate because we were particularly anxious, as a means of throwing further light on the reaction mechanism discussed above, to study the action of ammonia and a desulphurising agent on 1-*p*-chlorophenyl-5 : 5-dimethyl- and 1-*p*-chlorophenyl-5-methyl-5-*iso*propyl-dithiobiuret. It seemed possible that, in contrast to the corresponding 4-*iso*dithiobiurets, replacement of the 2-sulphur atom might occur to give the corresponding *N*-*p*-chlorophenyl-guanyl-*N*′*N*′-dimethyl- and *N*′-methyl-*N*′-*iso*propyl-thioureas, but that the reactions would not proceed further to give diguanides because of the absence, in either case, of a hydrogen atom on the nitrogen atom carrying the alkyl groups.

The methods used by Fullhart and ourselves for the preparation of 1-aryl-5-monoalkyldithiobiurets were based on the earlier syntheses of 1-aryl- and 1 : 5-diaryl-dithiobiurets by the condensation of aryl *iso*thiocyanates with *S*-alkyl*iso*thioureas and *N*-aryl-*S*-alkyl*iso*thioureas, respectively (cf. Johnson, *Amer. Chem. J.*, 1903, **30**, 167), followed by thiohydrolysis of the resulting 1-aryl- and 1 : 5-diaryl-4-alkyl-4-*iso*dithiobiurets (cf. Underwood and Dains, *Kansas Univ. Sci. Bull.*, 1937, **24**, 5). The reaction of arylamines with perthiocyanic acid (xanthan hydride) to give 1-aryldithiobiurets (for references see Part XXX, *loc. cit.*) cannot be modified to give the 5-alkyl compounds.

Previously, abortive attempts had been made to prepare 1-*p*-chlorophenyl-5-*iso*propyl-dithiobiuret by the direct interaction of *p*-chlorophenyl *iso*thiocyanate with *iso*propylthiourea, but no condensation occurred when the reactants were heated together in boiling xylene for ½ hour, in pyridine at 120°, or on fusion together at 170°. Likewise, the reaction of *iso*propyl *iso*thiocyanate with *p*-chlorophenylthiourea could not be effected.

Tursini (*Ber.*, 1884, **17**, 584) observed that 1-phenyldithiobiuret was alkylated with ethyl iodide in alcohol in presence of ammonia, and Johnson (*loc. cit.*) concluded that the product was 1-phenyl-2-ethyl-2-*iso*dithiobiuret (VI; R = R′ = H) since it was not identical with the 4-*S*-ethyl compound (III; R = R′ = R″ = H) prepared by interaction of phenyl *iso*thiocyanate with *S*-ethyl*iso*thiourea. Further proof has now been provided that alkylation of 1-aryldithiobiurets occurs first in the 2-position by the observation that 1-*p*-chlorophenyl-5-*iso*propyldithio-

biuret on treatment with ethyl iodide under Tursini's conditions must have given 1-p-*chlorophenyl*-2-*ethyl*-5-iso*propyl*-2-iso*dithiobiuret* (VI; R = Cl, R′ = Pr^i), since it was not only different from the 1-*p*-chlorophenyl-4-ethyl-5-*iso*propyl-4-*iso*dithiobiuret described above, but also gave N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide on treatment with alcoholic ammonia in presence of mercuric oxide.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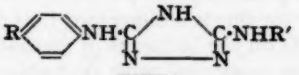
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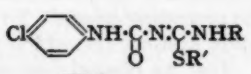
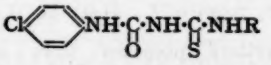
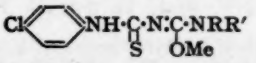

(IX.)

Johnson (*loc. cit.*) has shown that 1 : 5-diaryl-4-alkyl-4-*iso*dithiobiurets are further alkylated with methyl iodide to give 2 : 4-di-*S*-alkyl derivatives, *i.e.*, 1 : 5-diaryl-2 : 4-dialkyl-2 : 4-di*iso*dithiobiurets. Analogously, further alkylation of the 1-aryl-5-alkyl-4-*S*-ethyl*iso*dithiobiurets of type (III) with ethyl iodide in alcoholic solution in the cold led to compounds of the type (VII), from which we were able to prepare a number of 3-arylamino-5-alkylamino-1 : 2 : 4-triazoles of type (VIII) by reaction with hydrazine (cf. the preparation of 3-amino-5-arylamino-1 : 2 : 4-triazoles from 1-aryl-2 : 4-dialkyl-2 : 4-di*iso*dithiobiurets; Underwood and Dains, *loc. cit.*). In general, the intermediate 1-aryl-2 : 4 : 5-trialkyl-2 : 4-di*iso*dithiobiurets were obtained as oils, or low-melting solids, which were difficult to crystallise, although in one case, that of 1-*p*-chlorophenyl-5-*iso*propyl-2 : 4-diethyl-2 : 4-di*iso*dithiobiuret, the compound was isolated as its *hydriodide*. Usually, therefore, the crude compounds of type (VII) were caused to react directly with hydrazine in alcoholic solution. The compounds of type (VIII) prepared included 3-p-*chloroanilino*-5-iso*propylamino*-, -5-*methylamino*-, -5-*ethylamino*-, and -5-n-*butylamino*-1 : 2 : 4-*triazoles* and 3-p-*bromoanilino*-5-iso*propylamino*-1 : 2 : 4-*triazole*, but none showed any antimalarial activity when tested against *P. gallinaceum* in chicks, despite their apparent close similarity to the diguanides.

In the course of the investigations described in this series of papers we have continually attempted to relate antimalarial activity with chemical structure. Thus in Part XII (*J.*, 1947, 154) the suggestion was made that in the diguanides (I), and in the earlier pyrimidine types from which they were evolved, the possession of antimalarial activity was to be associated with the contribution to a resonance hybrid of the polarised form in which a conjugated path could be traced through alternate carbon and nitrogen atoms from the anilino-nitrogen to the nitrogen atom carrying the terminal alkyl- or dialkylaminoalkyl-group. On this basis the triazoles of type (VIII) might have been expected to exhibit activity.

Another suggestion which has been made (Curd and Rose, *Nature*, 1946, **158**, 707) to explain the antimalarial activity of the diguanide (I; R = Pr^i) was that it might be capable of interfering with a porphyrin-containing enzyme system essential to the malaria parasites, because of a similarity between the copper complex of the drug (containing two molecules of diguanide to one atom of copper, and assuming the symmetrical disposition of the diguanide molecules in a planar structure) and the metal protoporphyrins. Manifestly the triazoles (VIII) cannot form similarly constituted copper complexes, nor can they, through hydrogen-bond resonance such as is possible in the case of the diguanides (cf. Gage, Part XXXIV, this vol., p. 221), give a structure simulating a portion of the metal protoporphyrins.

(X.) 


(XI.)

The investigation was terminated with some miscellaneous experiments on monothiobiurets. It has been recorded in the preceding paper that *p*-chlorophenyl *iso*cyanate reacted with *ON*-dialkyl*iso*ureas to give 1-*p*-chlorophenyl-4 : 5-dialkyl-4-*iso*biurets which were hydrolysed to 1-*p*-chlorophenyl-5-alkylbiurets. Analogously, the same *iso*cyanate reacted with *NS*-dialkyl-*iso*thioureas, for instance with *NS*-diethyl*iso*thiourea and with *S*-ethyl-*N*-*iso*propyl*iso*thiourea, to give respectively 1-p-*chlorophenyl*-4 : 5-*diethyl*-4-iso*thiobiuret* (IX; R = R′ = Et) and 1-p-*chlorophenyl*-4-*ethyl*-5-iso*propyl*-4-iso*thiobiuret* (IX; R = Pr^i, R′ = Et), which on treatment with a boiling alcoholic solution of sodium hydrogen sulphide afforded the corresponding monothiobiurets, 1-p-*chlorophenyl*-5-*ethyl*- (X; R = Et) and -5-iso*propyl*-4-*thiobiuret* (X; R = Pr^i). Neither of these compounds exhibited any activity when tested against *P. gallinaceum* in chicks. Their constitution followed from the method of synthesis, but additional proof was provided by reaction of (X; R = Pr^i) with ammonia in presence of mercuric oxide whereby it was converted into *N*-*p*-chlorophenyl-*N*′-*iso*propylguanylurea (V; X = O,

R = Pr^{i}), identical with the compound made by condensation of *p*-chlorophenyl *iso*cyanate with *iso*propylguanidine (preceding paper).

It has been reported (Lakra and Dains, *J. Amer. Chem. Soc.*, 1929, **51**, 220) that 1-phenyl-4-thiobiuret was converted into 1-phenylbiuret by the action of lead monoxide in alcohol, but when 1-*p*-chlorophenyl-5-*iso*propyl-4-thiobiuret was treated with mercuric oxide in methanol it was converted into 1-*p*-chlorophenyl-4-methyl-5-*iso*propyl-4-*iso*biuret described in the preceding paper. To account for this it is suggested that desulphurisation to give a carbodiimide first occurs, which then adds on the elements of methanol.

Just as phenyl *iso*cyanate was condensed with *N*-*p*-chlorophenyl-*O*-methyl*iso*urea to give 1-phenyl-5-*p*-chlorophenyl-4-methyl-4-*iso*biuret (Part XLII, *loc. cit.*), *p*-chlorophenyl *iso*thiocyanate was condensed with the same compound to give 1 : 5-*di*-p-*chlorophenyl*-4-*methyl*-4-iso-2-*thiobiuret* (XI; R = H, R′ = C_6H_4Cl-*p*) and with the appropriate *O*-methyl-*N*-alkyl- or *NN*-dialkyl-*iso*ureas to give 1-p-*chlorophenyl*-4 : 5-*dimethyl*-5-iso*propyl*-, -4-*methyl*-5 : 5-*di*-n-*butyl*-, and -4-*methyl*-5-n-*butyl*-4-iso-2-*thiobiuret* (XI; R = H, R′ = Bu^{n}). None of these compounds was hydrolysed to the corresponding monothiobiuret in view of the inactivity of the compounds of type (X), but it was also shown that *p*-chlorophenyl *iso*cyanate condensed with *N*-*p*-chlorophenyl-*S*-methyl*iso*thiourea to give 1 : 5-*di*-p-*chlorophenyl*-4-*methyl*-4-iso-4-*thiobiuret* (IX; R = C_6H_4Cl-*p*, R′ = Me). Fullhart (*loc. cit.*) has reported the analogous condensation of phenyl *iso*cyanate with *N*-*p*-chlorophenyl-*S*-methyl*iso*thiourea and thiohydrolysis of the resulting 1-phenyl-5-*p*-chlorophenyl-4-methyl-4-*iso*-4-thiobiuret to give 1-phenyl-5-*p*-chlorophenyl-4-thiobiuret.

Experimental.

1-p-*Chlorophenyl*-4-*ethyl*-5-iso*propyl*-4-iso*thiobiuret* (III; R = Cl, R′ = H, R″ = Pr^{i}).—*S*-Ethyl-*N*-*iso*propyl*iso*thiourea hydrobromide (22·8 g.) (Part XXXVII, *loc. cit.*) was dissolved in a solution of potassium hydroxide (5·6 g.) in water (50 c.c.), and a solution of *p*-chlorophenyl *iso*thiocyanate (16·8 g.) in alcohol (50 c.c.) added. The mixture was stirred for 20 hours. The oil first formed gradually solidified. The product was then collected, dried, and crystallised from light petroleum (b. p. 100—120°) to give 1-p-*chlorophenyl*-4-*ethyl*-5-iso*propyl*-4-iso*dithiobiuret* (6281) as colourless prisms, m. p. 122—124° (Found: C, 49·8; H, 6·1; N, 13·3; S, 20·8. $C_{13}H_{18}N_3ClS_2$ requires C, 49·4; H, 5·7; N, 13·3; S, 20·3%).

1-p-*Chlorophenyl*-5-*methyl*-4-*ethyl*-4-iso*dithiobiuret*.—*N*-Methylthiourea (16·5 g.) was dissolved in alcohol (100 c.c.), ethyl bromide (22 g.) added, and the solution boiled under reflux for 20 hours. The reaction mixture was evaporated to dryness under reduced pressure and the residue stirred with ethyl acetate. The resulting crystalline *N*-methyl *S*-ethyl*iso*thiourea hydrobromide was collected and dried in a vacuum (yield, 31·35 g.). Because of its hygroscopic nature it was used directly, without further purification or analysis, for reaction with *p*-chlorophenyl *iso*thiocyanate, as described above, to give 1-p-*chlorophenyl*-5-*methyl*-4-*ethyl*-4-iso*dithiobiuret* as colourless flat prisms, m. p. 104—105° (Found: C, 46·0; H, 5·0; N, 14·7. $C_{11}H_{14}N_3ClS_2$ requires C, 45·9; H, 4·9; N, 14·6%) (6355).

1-p-*Chlorophenyl*-4 : 5-*diethyl*-4-iso*dithiobiuret*.—Prepared similarly from *NS*-diethyl*iso*thiourea hydrobromide (Part XXXVII, *loc. cit.*) and *p*-chlorophenyl *iso*thiocyanate, this *biuret* crystallised from light petroleum (b. p. 80—100°) as colourless prisms, m. p. 110—112° (Found: C, 47·7; H, 5·4; N, 13·7; S, 22·0. $C_{12}H_{16}N_3ClS_2$ requires C, 47·8; H, 5·3; N, 13·9; S, 21·3%) (6356).

1-p-*Chlorophenyl*-4-*ethyl*-5-n-*butyl*-4-iso*thiobiuret*.—*N*-*n*-Butylthiourea was treated with ethyl bromide as described above for *N*-methylthiourea. The resulting crude *S*-ethyl-*N*-*n*-butyl*iso*thiourea hydrobromide (12·1 g.) was dissolved in a solution of potassium hydroxide (2·8 g.) in water (50 c.c.), and a solution of *p*-chlorophenyl *iso*thiocyanate (8·5 g.) in alcohol (50 c.c.) added. The mixture was stirred at room temperature for 4 hours during which the oil first precipitated gradually solidified. The product was collected, washed with water, and dried in a vacuum. Crystallisation from light petroleum (b. p. 80—100°) gave 1-p-*chlorophenyl*-4-*ethyl*-5-n-*butyl*-4-iso*dithiobiuret* as colourless rhombs, m. p. 77—79° (Found: C, 51·2; H, 5·9; N, 12·3. $C_{14}H_{20}N_3ClS_2$ requires C, 51·0; H, 6·1; N, 12·7%) (6569).

1-m-*Chlorophenyl*-4-*ethyl*-5-iso*propyl*-4-iso*dithiobiuret*, similarly prepared from *m*-chlorophenyl *iso*thiocyanate (Hofmann, *Ber.*, 1880, **13**, 14) and *S*-ethyl-*N*-*iso*propyl*iso*thiourea hydrobromide, crystallised from light petroleum (b. p. 60—80°) as colourless prisms, m. p. 80—81° (Found: C, 48·9; H, 5·5; N, 13·8. $C_{13}H_{18}N_3ClS_2$ requires C, 49·4; H, 5·7; N, 13·3%) (6459).

1-p-*Bromophenyl*-4-*ethyl*-5-iso*propyl*-4-iso*dithiobiuret*, prepared analogously but from *p*-bromophenyl *iso*thiocyanate, crystallised from light petroleum (b. p. 100—120°) as colourless elongated prisms, m. p. 129—130° (Found: C, 43·2; H, 5·0; N, 11·6. $C_{13}H_{18}N_3BrS_2$ requires C, 43·3; H, 5·0; N, 11·7%).

1-p-*Iodophenyl*-4-*ethyl*-5-iso*propyl*-4-iso*dithiobiuret*, prepared similarly from *p*-iodophenyl *iso*thiocyanate (see Part XXIX, *loc. cit.*) and *S*-ethyl-*N*-*iso*propyl*iso*thiourea hydrobromide, crystallised from light petroleum (b. p. 100—120°) as colourless parallelepipeds, m. p. 124—125° (Found: C, 38·7; H, 5·0; N, 10·5. $C_{13}H_{18}N_3IS_2$ requires C, 38·3; H, 4·5; N, 10·3%) (6492).

1-3′ : 4′-*Dichlorophenyl*-4-*ethyl*-5-iso*propyl*-4-iso*dithiobiuret*, prepared in a similar manner from 3 : 4-dichlorophenyl *iso*thiocyanate (Dyson, George, and Hunter, *J.*, 1926, 3041), separated from light petroleum (b. p. 80—100°) as colourless laminæ, m. p. 104° (Found: C, 44·7; H, 4·9; N, 11·7. $C_{13}H_{17}N_3Cl_2S_2$ requires C, 44·55; H, 4·9; N, 12·0%).

1 : 5-*Di*-p-*chlorophenyl*-4-*methyl*-4-iso*dithiobiuret* (IV; R = H, R′ = C_6H_4Cl-*p*, R″ = Me).—*N*-*p*-Chlorophenyl-*S*-methyl*iso*thiourea (6·68 g.) (Part XXV, Crowther, Curd, and Rose, *J.*, 1948, 586) was dissolved in dry ether (50 c.c.), and a solution of *p*-chlorophenyl *iso*thiocyanate (5·65 g.) in dry ether

(50 c.c.) added. After standing for 3 days the solvent was evaporated and the residue crystallised first from chlorobenzene and then from 2-ethoxyethanol to give the product as colourless flat prisms, m. p. 158—160° (Found: C, 48·5; H, 3·6; N, 11·6; S, 17·8. Calc. for $C_{15}H_{13}N_3Cl_2S_2$: C, 48·6; H, 3·5; N, 11·3; S, 17·3%) (6254) (Fullhart, *loc. cit.*, gives m. p. 154—155°).

1-p-*Chlorophenyl*-5-iso*propyldithiobiuret* (II; R = Cl, R′ = H, R″ = Pr^i).—Sodium (0·92 g.) was dissolved in alcohol (25 c.c.), and hydrogen sulphide passed into the solution until the gain in weight was 1·36 g. This solution was added to a solution of 1-*p*-chlorophenyl-4-ethyl-5-*iso*propyl-4-*iso*dithiobiuret (6·3 g.) in alcohol (50 c.c.), and the mixture boiled under reflux for 1 hour while hydrogen sulphide passed through it. The hot reaction mixture was then carbon-treated, filtered, and acidified with acetic acid. On cooling, the product crystallised and was collected and recrystallised from light petroleum (b. p. 100—120°); colourless, long, flat prisms, m. p. 148° (Found: C, 45·8; H, 5·0; N, 14·4; S, 22·4. Calc. for $C_{11}H_{14}N_3ClS_2$: C, 45·9; H, 4·9; N, 14·6; S, 22·3%) (6337) (Fullhart, *loc. cit.*, quotes m. p. 135—137°).

1-p-*Chlorophenyl*-5-*methyldithiobiuret*, prepared similarly by thiohydrolysis of 1-*p*-chlorophenyl-5-methyl-4-ethyl-4-*iso*dithiobiuret, crystallised from toluene as colourless plates, m. p. 164—166° (Found: C, 42·0; H, 4·1; N, 16·1; S, 25·0. $C_9H_{10}N_3ClS_2$ requires C, 41·6; H, 3·9; N, 16·2; S, 24·7%) (6406).

1-p-*Chlorophenyl*-5-*ethyldithiobiuret*, similarly prepared from 1-*p*-chlorophenyl-4 : 5-diethyl-4-*iso*-dithiobiuret, crystallised from benzene as colourless minute prisms, m. p. 158—160° (Found: C, 43·8; H, 4·5; N, 15·4. $C_{10}H_{12}N_3ClS_2$ requires C, 43·85; H, 4·4; N, 15·3%) (6587).

1-p-*Chlorophenyl*-5-n-*propyldithiobiuret*.—*N*-*n*-Propylthiourea (18·9 g.) (Hecht, *Ber.*, 1890, **23**, 283) in alcohol (200 c.c.) was heated under reflux with ethyl bromide (20 g.) overnight, and the reaction mixture evaporated to dryness under reduced pressure. Without further purification the resulting *S*-ethyl-*N*-*n*-propyl*iso*thiourea hydrobromide was treated with potassium hydroxide to liberate the base, which was brought into reaction with *p*-chlorophenyl *iso*thiocyanate in aqueous-alcoholic solution, as described above in similar cases, to give 1-*p*-chlorophenyl-4-ethyl-5-*n*-propyl-4-*iso*dithiobiuret. Complete purification of this substance was difficult and so the crude material was thiohydrolysed in the usual way to give 1-p-*chlorophenyl*-5-n-*propyldithiobiuret*, which crystallised from light petroleum (b. p. 100—120°) as a colourless microcrystalline powder, m. p. 140—141° (Found: C, 46·3; H, 4·5; N, 14·7. $C_{11}H_{14}N_3ClS_2$ requires C, 45·9; H, 4·9; N, 14·6%) (6813).

1-p-*Chlorophenyl*-5-n-*butyldithiobiuret*, prepared as described for the corresponding 5-*iso*propyl compound but from 1-*p*-chlorophenyl-4-ethyl-5-*n*-butyl-4-*iso*dithiobiuret, crystallised from light petroleum (b. p. 100—120°) as colourless needles, m. p. 132—133° (Found: C, 47·7; H, 5·2; N, 13·8. $C_{12}H_{16}N_3ClS_2$ requires C, 47·8; H, 5·3; N, 13·9%) (6589).

1-m-*Chlorophenyl*-5-iso*propyldithiobiuret*, similarly prepared from 1-*m*-chlorophenyl-4-ethyl-5-*iso*propyl-4-*iso*dithiobiuret, crystallised from benzene–light petroleum (b. p. 60—80°) as colourless laminæ, m. p. 128—129° (Found: C, 46·0; H, 5·5; N, 15·0. $C_{11}H_{14}N_3ClS_2$ requires C, 45·9; H, 4·9; N, 14·6%) (6491).

1-p-*Bromophenyl*-5-iso*propyldithiobiuret*, prepared, as described for 6337, from the corresponding 4-*S*-ethyl compound, separated from benzene–light petroleum (b. p. 60—80°) as colourless flat prisms, m. p. 150—152° (Found: C, 39·8; H, 4·3; N, 12·4. $C_{11}H_{14}N_3BrS_2$ requires C, 39·8; H, 4·2; N, 12·6%) (6493).

1-p-*Iodophenyl*-5-iso*propyldithiobiuret*, prepared similarly from 1-*p*-iodophenyl-4-ethyl-5-*iso*propyl-4-*iso*dithiobiuret, crystallised from benzene–light petroleum (b. p. 60—80°) as colourless elongated prisms, m. p. 136—138° (Found: C, 34·9; H, 3·9; N, 11·1. $C_{11}H_{14}N_3IS_2$ requires C, 34·8; H, 3·7; N, 11·1%) (6568).

1-3′ : 4′-*Dichlorophenyl*-5-iso*propyldithiobiuret*, prepared in an analogous manner from 1-3′ : 4′-dichlorophenyl-4-ethyl-5-*iso*propyl-4-*iso*dithiobiuret, crystallised from benzene as colourless felted needles, m. p. 158° (Found: C, 41·4; H, 4·1; N, 12·8. $C_{11}H_{13}N_3Cl_2S_2$ requires C, 41·0; H, 4·1; N, 13·0%).

Reaction of 1-p-*Chlorophenyl*-5-iso*propyldithiobiuret with Ammonia and Mercuric Oxide*.—1-*p*-Chlorophenyl-5-*iso*propyldithiobiuret (2·85 g.), mercuric oxide (8·68 g.), and saturated alcoholic ammonia (100 c.c.) were stirred together at room temperature for 20 hours. The reaction mixture was then filtered and evaporated to dryness under diminished pressure. The residue was dissolved in acetone, and the solution made acid to litmus with acetic acid. The crystalline material precipitated was collected and crystallised from alcohol–acetone to give N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide acetate, m. p. and mixed m. p. 184—185°.

Reaction of 1-p-*Chlorophenyl*-4-*ethyl*-5-iso*propyl*-4-iso*dithiobiuret with Ammonia and Mercuric Oxide*.—1-*p*-Chlorophenyl-4-ethyl-5-*iso*propyl-4-*iso*dithiobiuret (3·15 g.), mercuric oxide (8·68 g.), and saturated alcoholic ammonia (50 c.c.) were stirred together at 30—35° for 20 hours, and the mixture filtered and evaporated to dryness under reduced pressure. The residue was extracted with warm 2N-hydrochloric acid, the extract carbon-treated, filtered, and made just alkaline to brilliant-yellow with ammonia. The precipitated solid was collected and crystallised from water to give N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide hydrochloride, m. p. 243—244°, undepressed in admixture with an authentic specimen.

Reaction of 1-p-*Chlorophenyl*-5-*methyldithiobiuret with Ammonia and Mercuric Oxide*.—The dithiobiuret (2·6 g.), mercuric oxide (8·68 g.), and saturated alcoholic ammonia (100 c.c.) were stirred at 30—35° for 20 hours and the mixture worked up as in the preceding experiment to give N^1-*p*-chlorophenyl-N^5-methyldiguanide hydrochloride, m. p. 227—228° either alone or in admixture with authentic material.

Reaction of 1-p-*Chlorophenyl*-4-*methyl*-4-iso*dithiobiuret with* iso*Propylamine*.—1-*p*-Chlorophenyl-4-methyl-4-*iso*dithiobiuret (1 g.) (Part XXX, *loc. cit.*) and *iso*propylamine (5 c.c.) were heated together at 60° for 2 hours. The mixture was then poured into water and kept until the product solidified. Collected and crystallised from benzene, it formed colourless small flat prisms, m. p. 143°, undepressed in admixture with *N*-*p*-chlorophenyl-*N′*-*iso*propylguanylthiourea prepared as described in Part XXIX (*loc. cit.*).

Reaction of 1-p-*Chlorophenyl*-4-*methyl*-4-iso*dithiobiuret with Methylamine*.—The dithiobiuret (6 g.), methylamine (20 c.c. of 21% aqueous solution), and alcohol (10 c.c.) were shaken together overnight at room temperature. The starting material gradually dissolved and was replaced by a granular product.

This was collected, washed with water, dried, and crystallised from ethyl acetate–light petroleum (b. p. 60—80°) to give N-p-*chlorophenyl*-N′-*methylguanylthiourea* as colourless rhombic crystals, m. p. 130—132° (Found: C, 44·3; H, 4·3; S, 13·2. $C_9H_{11}N_4ClS$ requires C, 44·5; H, 4·6; S, 13·2%).

Reaction of 1-p-*Chlorophenyl*-4-*methyl*-4-iso*dithiobiuret with Ammonia*.—1-*p*-Chlorophenyl-4-methyl-4-*iso*dithiobiuret (2 g.) and saturated methanolic ammonia (20 c.c.) were heated at 50—60° for 10 hours. The mixture was then filtered and the filtrate poured into water. The precipitated crystalline material was collected, dried, and crystallised first from benzene–alcohol and then from xylene–butanol to give *N*-*p*-chlorophenyl-*N*′-guanylthiourea, m. p. 195°, either alone or in admixture with material prepared as in Part XXXVII (*loc. cit.*).

1-p-*Chlorophenyl*-5 : 5-*dimethyl*-4-*ethyl*-4-iso*dithiobiuret* (IV; R = R′ = Me, R″ = Et).—*NN*-Dimethylthiourea (5·2 g.) (Wallach, *Ber.*, 1899, **32**, 1874), alcohol (150 c.c.), and ethyl bromide (12 g.) were allowed to stand together for 3 days and the solution then evaporated to dryness under reduced pressure. The residual oil readily solidified and consisted substantially of NN-*dimethyl*-S-*ethyliso*thiourea *hydrobromide*. A sample crystallised from alcohol–ethyl acetate had m. p. 142—143° (Found: C, 27·6; H, 6·0; S, 15·1. $C_5H_{12}N_2S,HBr$ requires C, 28·1; H, 6·1; S, 15·0%). 6·89 G. of this were added to a solution of potassium hydroxide (1·68 g.) in water (50 c.c.), followed by a solution of *p*-chlorophenyl *iso*thiocyanate (5·05 g.) in alcohol (50 c.c.). The precipitated product was collected and crystallised, first from alcohol and then from benzene, to give 1-p-*chlorophenyl*-5 : 5-*dimethyl*-4-*ethyl*-4-iso*dithiobiuret* as colourless prisms, m. p. 172—174° (Found: C, 47·8; H, 4·8. $C_{12}H_{16}N_3ClS_2$ requires C, 47·8; H, 5·3%).

N-*Methyl*-N-iso*propylthiourea*.—Hydrogen sulphide was passed into a solution of methyl*iso*propylcyanamide (20 g.) (Part XXXIII, Ainley, Curd, and Rose, this vol., p. 98) in alcohol (50 c.c.) saturated with ammonia. When precipitation had visibly ceased, the reaction mixture was kept for 3 days and then evaporated to dryness under reduced pressure. The residual solid crystallised from water to give N-*methyl*-N-iso*propylthiourea* as colourless leaves, m. p. 100—102° (Found: C, 44·9; H, 8·9; N, 20·7. $C_5H_{12}N_2S$ requires C, 45·4; H, 9·2; N, 21·2%).

Ethyl bromide (6·0 g.) was added to a solution of *N*-methyl-*N*-*iso*propylthiourea (6·6 g.) in dry alcohol (50 c.c.), and the mixture kept overnight. After evaporation under reduced pressure, the residue was stirred with ethyl acetate and filtered to give *N*-methyl-*S*-ethyl-*N*-*iso*propyl*iso*thiourea hydrobromide, m. p. 130—132° (not analysed).

1-p-*Chlorophenyl*-5-*methyl*-4-*ethyl*-5-iso*propyl*-4-iso*dithiobiuret* (IV; R = Me, R′ = Pr^i, R″ = Et).—Prepared from *p*-chlorophenyl *iso*thiocyanate and *N*-methyl-*S*-ethyl-*N*-*iso*propyl*iso*thiourea hydrobromide, as described above in similar cases, this *biuret* crystallised from light petroleum (b. p. 100—120°) as colourless prisms, m. p. 126° (Found: C, 51·2; H, 6·1; N, 12·7. $C_{14}H_{20}N_3ClS_2$ requires C, 51·0; H, 6·1; N, 12·7%).

1-p-*Chlorophenyl*-2-*ethyl*-5-iso*propyl*-2-iso*dithiobiuret* (VI; R = Cl, R′ = Pr^i).—1-*p*-Chlorophenyl-5-*iso*propyldithiobiuret (8·61 g.), ethyl iodide (5·15 g.), alcohol (150 c.c.), and ammonia (3 c.c.) were mixed and kept for 3 days. Evaporation of the solution under diminished pressure and crystallisation of the residue from alcohol gave the *product*, which was recrystallised from light petroleum (b. p. 60—80°); clusters of colourless prisms, m. p. 82—84° (Found: C, 49·3; H, 5·6; N, 13·7. $C_{13}H_{18}N_3ClS$ requires C, 49·4; H, 5·7; N, 13·3%).

Reaction of 1-p-*Chlorophenyl*-2-*ethyl*-5-iso*propyl*-2-iso*dithiobiuret with Ammonia and Mercuric Oxide*.—The preceding compound (2·55 g.), mercuric oxide (7·1 g.), and saturated alcoholic ammonia (50 c.c.) were stirred together at 30—35° for 20 hours. The mixture was then filtered and evaporated to dryness under diminished pressure. The residue was extracted with hot 2N-hydrochloric acid, and the extract filtered from a little insoluble matter and made faintly alkaline to brilliant-yellow with ammonia. Addition of a little salt induced separation of the product, which was collected, crystallised from water, and identified as N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide hydrochloride, m. p. and mixed m. p. 243—244°.

1-p-*Chlorophenyl*-2 : 4-*diethyl*-5-iso*propyl*-2 : 4-*di*iso*dithiobiuret* (VII; R = Cl, R′ = Pr^i).—A solution of 1-*p*-chlorophenyl-4-ethyl-5-*iso*propyl-4-*iso*dithiobiuret (6·3 g.) in alcohol (75 c.c.) was treated with ethyl iodide (6·24 g.) and the mixture kept for 4 days. It was then warmed until homogeneous, more ethyl iodide (6·24 g.) and alcohol (25 c.c.) added, and the whole set aside for a further 24 hours and then evaporated to dryness under diminished pressure. The residue solidified on standing overnight and was crystallised from alcohol–ether to give 1-p-*chlorophenyl*-2 : 4-*diethyl*-5-iso*propyl*-2 : 4-*di*iso*dithiobiuret hydriodide* as colourless prisms, m. p. 134—136° (Found: C, 37·9; H, 4·5; N, 9·4. $C_{15}H_{22}N_3ClS,HI$ requires C, 38·2; H, 4·9; N, 8·9%) (6595).

The corresponding base liberated from the hydriodide by stirring with sodium carbonate solution and isolated by extraction with ether formed a low-melting (*ca.* 40°) solid.

3-p-*Chloroanilino*-5-iso*propylamino*-1 : 2 : 4-*triazole* (VIII; R = Cl, R′ = Pr^i).—The above base (2·75 g.) was dissolved in alcohol (20 c.c.), hydrazine hydrate (2·2 c.c.) added, and the mixture heated under reflux for 4 hours. The *triazole* which separated on cooling and dilution with water was collected and crystallised from benzene; colourless laminæ, m. p. 162—164° (Found: C, 52·5; H, 5·5; N, 27·4. $C_{11}H_{14}N_5Cl$ requires C, 52·5; H, 5·6; N, 27·8%) (6488).

3-p-*Chloroanilino*-5-*methylamino*-1 : 2 : 4-*triazole*.—1-*p*-Chlorophenyl-5-methyl-4-ethyl-4-*iso*dithiobiuret was treated with ethyl iodide in alcohol as described above to give 1-*p*-chlorophenyl-5-methyl-2 : 4-diethyl-2 : 4-di*iso*dithiobiuret as an oil. This oil (8·58 g.) was boiled under reflux for 4 hours with alcohol (50 c.c.) containing hydrazine hydrate (7·9 c.c. of 35%). The product, which separated on cooling, was collected and crystallised from aqueous 2-ethoxyethanol to give the *triazole* as colourless elongated prisms, m. p. 261—263° (Found: C, 48·4; H, 4·6; N, 30·9. $C_9H_{10}N_5Cl$ requires C, 48·3; H, 4·5; N, 31·3%) (6442).

3-p-*Chloroanilino*-5-*ethylamino*-1 : 2 : 4-*triazole*, prepared similarly from 1-*p*-chlorophenyl-4 : 5-diethyl-4-*iso*dithiobiuret by *S*-ethylation followed by reaction with hydrazine, crystallised from aqueous 2-ethoxyethanol as colourless elongated flat prisms, m. p. 228—230° (Found: C, 50·5; H, 4·7; N, 29·2. $C_{10}H_{12}N_5Cl$ requires C, 50·5; H, 5·1; N, 29·5%) (6588).

3-p-*Chloroanilino*-5-n-*butylamino*-1 : 2 : 4-*triazole*, similarly prepared from 1-*p*-chlorophenyl-4-ethyl-

5-*n*-butyl-4-*iso*dithiobiuret, separated from alcohol in the form of elongated flat prisms, m. p. 196—198° (Found: C, 54·1; H, 5·7; N, 26·7. $C_{12}H_{16}N_5Cl$ requires C, 54·2; H, 6·1; N, 26·4%) (6614).

3-p-*Bromoanilino*-5-iso*propylamino*-1 : 2 : 4-*triazole*, likewise synthesised from 1-*p*-bromophenyl-4-ethyl-5-*iso*propyl-4-*iso*dithiobiuret, crystallised from chlorobenzene as colourless prisms, m. p. 154—156° (Found: C, 45·0; H, 4·7; N, 23·4. $C_{11}H_{14}N_5Br$ requires C, 44·6; H, 4·8; N, 23·6%) (6626).

1-p-*Chlorophenyl*-4 : 5-*diethyl*-4-iso*thiobiuret* (IX; R = R′ = Et).—A solution of potassium hydroxide (3·7 g.) in water (20 c.c.) was added to a solution of *NS*-diethyl*iso*thiourea hydrobromide (15·16 g.) in water (80 c.c.), and the mixture extracted with ether. To the dried ethereal solution a solution of *p*-chlorophenyl *iso*cyanate (9·2 g.) in ether (50 c.c.) was added. When the ensuing reaction was complete the solvent was evaporated off, and the residue crystallised from light petroleum (b. p. 80—100°) to give the *thiobiuret* as colourless elongated prisms, m. p. 122—124° (Found: C, 50·2; H, 5·4; N, 15·3. $C_{12}H_{16}ON_5ClS$ requires C, 50·4; H, 5·6; N, 14·7%) (6427).

The 4-*ethyl*-5-iso*propyl* analogue, prepared similarly from *p*-chlorophenyl *iso*cyanate and *S*-ethyl-*N*-*iso*propyl*iso*thiourea hydrobromide, separated from light petroleum (b. p. 80—100°) as colourless thin prisms, m. p. 132° (Found: C, 51·5; H, 5·8; N, 13·9. $C_{13}H_{18}ON_5ClS$ requires C, 52·1; H, 6·0; N, 14·0%) (6408).

1-p-*Chlorophenyl*-5-*ethyl*-4-*thiobiuret* (X; R = Et).—Sodium (0·9 g.) was dissolved in alcohol (50 c.c.), and hydrogen sulphide passed through the mixture until the gain in weight was 1·4 g. The resulting solution was added to a suspension of (IX; R = R′ = Et) (6 g.) in alcohol (50 c.c.), and the mixture boiled under reflux for 1 hour with the passage of hydrogen sulphide. The resulting solution was carbon-treated, filtered, and acidified with acetic acid. Addition of water precipitated the *thiobiuret*, which was collected, washed with water, dried, and crystallised from chlorobenzene; colourless flat needles, m. p. 184° (efferv.) (Found, in material dried in a vacuum at 80°: C, 46·3; H, 4·8; N, 16·3. $C_{10}H_{13}ON_5ClS$ requires C, 46·6; H, 4·7; N, 16·3%) (6949).

1-p-*Chlorophenyl*-5-iso*propyl*-4-*thiobiuret*, similarly prepared from (IX; R = Pr^i, R′ = Et (by thiohydrolysis, separated from benzene as colourless flat needles, m. p. 176—178° (Found: N, 15·5. $C_{11}H_{14}ON_5ClS$ requires N, 15·5%) (8607).

Reaction of 1-p-*Chlorophenyl*-5-iso*propyl*-4-*thiobiuret with Ammonia and Mercuric Oxide*.—The preceding compound (1·36 g.), mercuric oxide (4·3 g.), and saturated alcoholic ammonia (100 c.c.) were stirred together at 30—35° for 2 hours. After standing overnight, the mixture was filtered and evaporated to dryness. The solid residue crystallised from benzene to give *N*-*p*-chlorophenyl-*N*′-*iso*propylguanylurea, m. p. 130—132° undepressed in admixture with material prepared as described in the preceding paper.

Reaction of 1-p-*Chlorophenyl*-5-iso*propyl*-4-*thiobiuret with Methanol and Mercuric Oxide*.—A mixture of (X; R = Pr^i) (1·2 g.), mercuric oxide (2·1 g.), and methanol (100 c.c.) was boiled under reflux for 1 hour, then filtered hot, and the filtrate evaporated to dryness. The residue crystallised from aqueous methanol to give 1-*p*-chlorophenyl-4-methyl-5-*iso*propyl-4-*iso*biuret, m. p. 82—84° undepressed in admixture with authentic material (Part XLII).

1 : 5-*Di*-p-*chlorophenyl*-4-*methyl*-4-iso-2-*thiobiuret* (XI; R = H, R′ = C_6H_4Cl-*p*).—*p*-Chlorophenyl-*iso*thiocyanate (5·1 g.), dissolved in ether (25 c.c.), was added to a solution of *N*-*p*-chlorophenyl-*O*-methyl*iso*urea (5·5 g.) in ether (25 c.c.), and the whole kept for 3 days; light petroleum (b. p. 40—60°) was then added, and the precipitated solid filtered off. The mother-liquors were evaporated to dryness, leaving a solid residue. The combined solids were crystallised from benzene–light petroleum (b. p. 60—80°) to give the *thiobiuret* as colourless prisms, m. p. 143—145° (Found: C, 51·1; H, 3·6; N, 12·0. $C_{15}H_{13}ON_5Cl_2S$ requires C, 50·85; H, 3·7; N, 11·9%) (6441).

1-p-*Chlorophenyl*-4 : 5-*dimethyl*-5-iso*propyl*-4-iso-2-*thiobiuret*.—p-Chlorophenyl *iso*thiocyanate (5·1 g.), *ON*-dimethyl-*N*-*iso*propyl*iso*urea (3·9 g.), and water (25 c.c.) were mixed and warmed on the steam-bath for 10 minutes. After standing overnight, the solid product was collected, washed with water, and dried. Crystallisation from benzene gave the *thiobiuret* as minute colourless prisms, m. p. 147° (Found: C, 52·3; H, 6·1; N, 14·4. $C_{13}H_{18}ON_5ClS$ requires C, 52·1; H, 6·0; N, 14·0%) (6374).

O-*Methyl*-NN-*di*-n-*butyliso*urea.—Sodium (8·5 g.) was dissolved in dry methanol (125 c.c.), di-*n*-butylcyanamide (52 g.) added, and the mixture stirred at 50—60° for 2 hours. After cooling and dilution with water, hydrochloric acid was added to render the solution just acid, and the mixture extracted with ether. The aqueous layer was made alkaline with sodium hydroxide, and the precipitated product extracted with benzene. Evaporation of the dried (K_2CO_3) benzene extract then gave O-*methyl*-NN-*di*-n-*butyliso*urea as a colourless oil, b. p. 122°/18 mm. (Found: N, 15·2. $C_{10}H_{22}ON_2$ requires N, 15·0%).

1-p-*Chlorophenyl*-4-*methyl*-5 : 5-*di*-n-*butyl*-4-iso-2-*thiobiuret* (XI; R = R′ = Bu^n), prepared as described for 6374 from *p*-chlorophenyl *iso*thiocyanate and *O*-methyl-*NN*-di-*n*-butyl*iso*urea, crystallised from alcohol as colourless parallelepipeds, m. p. 124—126° (Found: C, 57·4; H, 7·3; N, 12·1. $C_{17}H_{26}ON_5ClS$ requires C, 57·4; H, 7·4; N, 11·8%) (6314).

The *monobutyl* analogue, prepared similarly from *p*-chlorophenyl *iso*thiocyanate and *O*-methyl-*N*-*n*-butyl*iso*urea, crystallised from light petroleum (b. p. 80—100°) as colourless prisms, m. p. 94—96° (Found: C, 52·4; H, 6·1; N, 14·0. $C_{13}H_{18}ON_5ClS$ requires C, 52·1; H, 6·0; N, 14·0%) (6357).

1 : 5-*Di*-p-*chlorophenyl*-4-*methyl*-4-iso*thiobiuret* (IX; R = C_6H_4Cl-*p*, R′ = Me).—*p*-Chlorophenyl *iso*cyanate (7·67 g.), dissolved in ether (25 c.c.), was added to a solution of *N*-*p*-chlorophenyl-*S*-methyl*iso*thiourea (10·02 g.) in ether (20 c.c.). Heat was evolved, and on standing a crystalline product separated. Collected and crystallised from benzene, this *thiobiuret* formed colourless thin prisms, m. p. 139—140° (Found: C, 50·7; H, 3·6; N, 11·8. $C_{15}H_{13}ON_5Cl_2S$ requires C, 50·85; H, 3·7; N, 11·9%) (6409).

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373. *The Molecular Weight and Limiting Density of Propane.*

By F. L. Casado, D. S. Massie, and R. Whytlaw-Gray.

Propane in a highly purified state has been prepared and its density compared with that of pure oxygen at 20·76° c. and at pressures of 700 and 350 mm. using a silica-fibre buoyancy microbalance.

The main object of the work was to see whether an exact value for the molecular weight of this gas could be obtained by a linear extrapolation of these ratios to zero pressure.

Although the PV–P isothermals at pressures below 1 atmosphere are for the permanent gases linear within very small limits; gases such as propane might be expected to show a slight curvature and if this were significant linear extrapolation would give too low a value for the limiting ratio and molecular weight. Actually the values found for the molecular weight of propane agree so closely with the figure from international atomic weights that it is concluded that any deviation from linearity is for this gas less than the errors of experiments. Direct compressibility measurements made at the same time support this view.

Adsorption which might affect the accuracy of the results has been measured and shown to have no appreciable effect on the final figure for the molecular weight which is 44·096.

Few determinations of high accuracy have been made in recent years of the limiting densities and molecular weights of so-called liquefiable gases, *i.e.*, gases which at room temperature are well below their critical temperatures. The most recent are those of Moles for ammonia, hydrogen sulphide, sulphur dioxide, and silicon tetrafluoride, for which he employed a very refined technique (*Trans. Faraday Soc.*, 1939, **35**, 1440; "Determination Physico-chimique des Poids Molec. et Atomique des Gaz," Collection Scientifique, Institut Internat. Co-operation Intellectuelle, Paris, 1938, pp. 1 and 74), and that for methyl ether carried out by Casado (Thesis, University of Santiago, 1943). In both, the densities were determined at a series of pressures from 1 to 0·25 atmosphere and were found to follow a straight line within close limits. For methyl ether Casado also made a series of direct compressibility determinations of from 1 atmosphere to about 200 mm. and obtained evidence of a strictly linear relation between PV and P. These and also the earlier experimental results of Cawood and Patterson (*J.*, 1933, 619) would seem to justify a straight-line extrapolation to zero pressure for liquefiable gases.

Moles's results have been criticised by Keesom on theoretical grounds (Determination Physico-chimique etc., p. 165), who calculates that the density–pressure graphs for the gases in question should shew a slight curvature towards the pressure axis and hence concludes that Moles's data should lead to slightly higher molecular weights.

The limiting-pressure method (Cawood and Patterson, *Phil. Trans.*, 1936, *A*, **236**, 77) and Whytlaw-Gray, Patterson, and Cawood (*Proc. Roy. Soc.*, 1931, *A*, **134**, 7) using a silica-fibre buoyancy microbalance has also been applied to the determination of the molecular weights of liquefiable gases, *i.e.*, xenon and hydrogen sulphide (see *ibid.*, p. 96), but, although the results obtained accord closely with the mass-spectrograph values, they are hardly accurate enough to throw much light on the question of curvature.

Although theory clearly indicates that at some temperature between the critical temperature and the boiling point a significant curvature in the low-pressure PV–P isothermals is to be expected, it has not so far been detected in any modern investigation, and all the evidence so far supports the contention of Moles that even for liquefiable gases at 0° c. a strictly linear extrapolation is applicable.

The object then of the present work was to determine accurately the molecular weight of propane by the limiting-pressure method, in order to see (*a*) of what degree of accuracy this method was capable and (*b*) whether the molecular weight so calculated exhibited any definite divergence from the true molecular weight which would indicate a slight curvature in the PV–P isothermal.

Experimental.

Microbalance.—The silica-fibre buoyancy microbalance used in this work is similar to the type described previously by Whytlaw-Gray, Patterson, and Cawood, and by Cawood and Patterson (*locc. cit.*). It was, however, of rather larger dimensions, carrying a suspended buoyancy bulb of 8·7 c.c., which reduced the ratio of surface to volume from 1 to 0·6. This buoyancy bulb was counterpoised at the other end of the 8-cm.-long beam by a smaller bulb with a hole in it, of very nearly the same weight, and the internal and external surfaces of which were together of approximately the same size as the external surface of the larger sealed bulb. By this means adsorption effects were compensated. Actually to get two bulbs of nearly equal weight and of such a size that their radii are in the ratio of $\sqrt{2} : 1$ was not easy. The bulbs were taken from a batch of small and large bulbs blown by Messrs. Cowlishaw and Co. of Manchester. The bulbs were measured and weighed, and a pair was selected which matched most closely.

Previously a flat plate had been used for surface compensation, but, since adsorption is apt to vary

with the type of surface, it was thought that two blown bulbs offered a greater chance of equality. By measuring the finished balance it was estimated that the difference in surface moments computed from the geometric areas on either side of the fibre suspension was, at most, 10%.

The beam was constructed from 1-mm.-diameter vitreous-silica rod, slung between uprights on a transverse silica fibre. The uprights were carried by a silica framework made from 4-mm.-diameter rod, as shown in Fig. 1. The only operation in construction which presented difficulty and which has not been described before is the fixing of the fibre suspension. This was done as follows. The beam and its sealed-on adsorption bulb *BB*, and the supporting frame *AA*, having been made separately, the former

FIG. 1.

Microbalance.

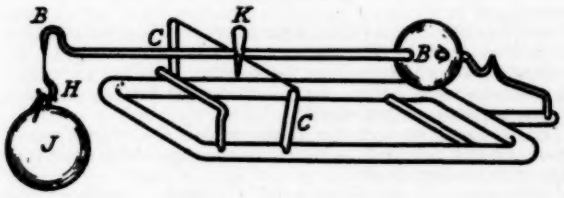
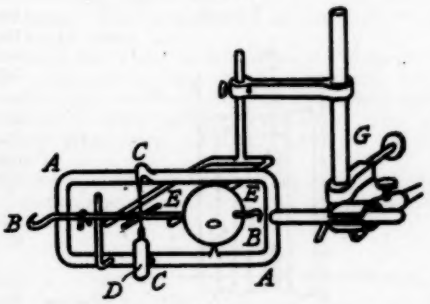


FIG. 2.



was sealed to one of the frame uprights *CC* by a very thin silica rod, the frame itself being clamped in a vertical position (Fig. 2). A silica weight *D* was then sealed by a similar fine rod to the lower upright below the beam. The upper rod was next heated in the oxy-coal-gas blowpipe, being drawn out little by little into a fine fibre. During this process the beam was kept in position by resting on a double-pronged silica support *EE* which could be moved up or down by means of a delicate rackwork *G*. When the upper fibre had been drawn out to a suitable length and fineness, the lower rod was heated, drawn out into a fibre, and sealed to the lower frame upright. After removal of the pronged support, the balance and frame were next cautiously turned through a right angle to the horizontal position, and the hook and terminal fibre *H* for suspending the buoyancy bulbs were made by a similar procedure.

The balance was now ready for adjustment. It was placed under a bell jar after approximate equilibrium had been obtained by adding small weights to the buoyancy bulb hook. Then by altering the air pressure the beam was balanced to float, and its period of swing observed. By adding small amounts of silica to the piece *K* in the centre of the beam, or by removing small amounts from it, the centre of gravity could be raised or lowered until the period of swing indicated a suitable sensitivity. By raising the centre of gravity until the beam is just unstable and then volatilising small amounts of silica from *K*, it is possible, with a balance of the dimensions described, to get a period as slow as 50 seconds. It is better, however, to work with a lower sensitivity and a period of about 20 seconds.

Such a balance will easily detect a pressure change less than 0·01 mm. in air, and indeed throughout our work the balance was more sensitive than the pressure reading. When finally adjusted, it was heated in an electric furnace at 400° for some hours in dry and dust-free air and was then transferred to its glass case inside a thermostatted water-tank. The glass case was connected to the manometer and the rest of the apparatus through glass spirals which served to protect the balance from vibration and to prevent grease spray (from the taps) entering the case. The balance was approximately on the same level as the lower chamber of the manometer.

The limiting-pressure method has often been described, and it will be sufficient to say here that it consists in comparing the balancing pressures of the standard gas, oxygen, and some other gas, in this case propane, at two different densities. By the addition or removal of small weights from the suspended hook of the microbalance carrying the buoyancy bulb, the balance can be adjusted to float at any desired density. From the ratios so obtained the limiting ratio is calculated by linear extrapolation and the molecular weight obtained.

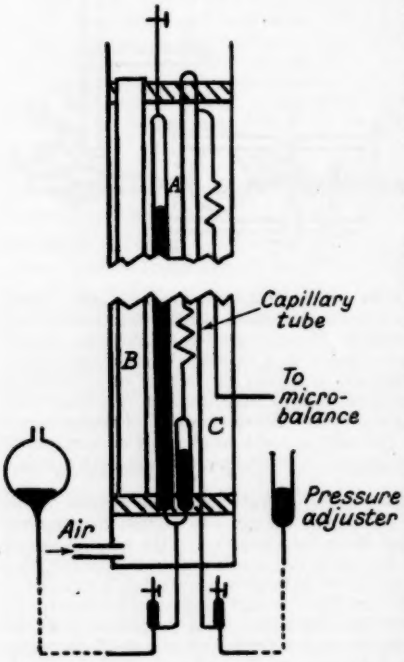
Since the main factor which limits accuracy, assuming adequate temperature control, is the pressure measurement, special care was taken to make the pressure readings as exact as possible.

Pressure.—The pressure was measured on a mercury manometer *A* (Fig. 3) contained in a thermostatted water-tank. Readings were taken by means of a cathetometer focussing on the mercury meniscus and then swinging through a small angle to focus on a Cowlishaw glass scale *B*, placed alongside the mercury column, in the water-tank. Moveable screens were arranged to slide behind the mercury column, touching the glass; and, by placing the screens so that only a small slit of light was visible between the meniscus and screen, errors due to reflection and refraction could be minimised and a clear image seen through the telescope. The two telescopes used were fitted with micrometer eyepieces so that the pressure could be read accurately to 0·01 mm. The manometer tube was constructed of 2·4-cm.-diameter tubing, to eliminate effects due to varying meniscus height (Whytlaw-Gray and Teich, *Trans. Faraday Soc.*, 1948, **44**, 774). Also on account of this, the pressure was always read with a rising meniscus in both limbs. As a fine adjustment to the pressure, the mercury in the capillary tube *C* could be raised or lowered.

Fig. 3 shows the manometer and connections. The fine tube above the lower limb of the manometer prevents the mercury, when raised suddenly, from flowing into the balance case. Glass spirals are included to reduce strain and vibrations.

The two tanks were thermostatted independently with the usual toluene regulator and electronic relay. The water was circulated in the tank containing the balance by a stirrer attached to a small motor. The temperature was read on a Beckmann thermometer the bulb of which was placed as close as possible to the balance case. It remainded constant within 0·005° over the period of a reading. Another thermometer in a different part of the bath was used as a check on the adequacy of the stirring. The stirring of the manometer tank presented greater difficulty, as a very long spindled stirrer was necessary to reach the bottom of the tank. The vibrations set up by this arrangement were found seriously to affect the setting of the balance. Eventually it was found that adequate stirring could be obtained by a continuous blast of air, from the compressed-air supply, blown through a pipe let into the base of the tank. The temperature was read on an ordinary mercury thermometer to 0·01°.

FIG. 3.



The two tanks containing the manometer and the microbalance were erected on a stone table in a basement room, so as to avoid vibration as far as possible. The microbalance tank was further protected by resting on thick rubber bungs.

Care was taken to avoid, as far as practicable, unjacketted connections outside the tanks. As finally arranged, the manometer was connected to the balance case by an 8-cm.-long glass tube of 2-mm. bore outside the tanks, and this was lagged with cotton wool.

The temperatures in the tanks were very nearly equal, that of the balance tank being on an average 20·76°, and that of the manometer 20·90°.

Preparation of the Gases.—(a) *Propane.* Initially the propane was obtained from a cylinder supplied by I.C.I. as 98—99% pure. This gas contained up to 1·5% of butane and up to 0·5% of ethane. We found that it also contained unsaturated hydrocarbons, mainly propylene and possibly *cyclo*propane.

We are indebted to Dr. Atack and Dr. McCormack, who were using the gas in quantity for their own researches in this Department, for kindly carrying out for us a preliminary fractionation and for supplying us with a middle fraction which formed our starting material.

This sample was then subjected to chemical treatment and finally further fractionation, since the boiling points of propylene (−47°) and propane (−44·5°) lie so close together. The gas was first passed through conc. potassium permanganate solution made slightly alkaline, contained in a tower and U-tube filled with glass beads, for the removal of the unsaturated compounds. It was then dried by a soda-lime tube and passed through a second tower containing fuming sulphuric acid, and two U-tubes containing concentrated sulphuric acid activated with silver sulphate as a catalyst. The gas was finally dried (P_2O_5), and about 40 c.c. were condensed in a vessel surrounded with liquid air. About a third of this liquid was allowed to evaporate and was rejected. The second fraction was condensed at the foot of a fractionating column, and the remaining fraction also rejected. In this way the lighter impurities such as ethane (b.p. −88°), and heavier compounds such as butane (b.p. −0·6°), were mostly eliminated.

The fractionating column, about 20 cm. long, contained a copper spiral and was constructed after the method of Booth and Swinehardt (*J. Amer. Chem. Soc.*, 1935, **57**, 1934). The top of the column was cooled with a mixture of solid carbon dioxide and alcohol. When the liquid was refluxing vigorously and a steady state had been reached, small fractions of gas were taken off so as to maintain a steady pressure of about 350 mm. in the gauge. The various fractions were subsequently stored in evacuated bulbs.

The balancing pressures of the various fractions were then determined with the microbalance. A very large number of determinations was made, and the results were compared as a test of purity. When agreement was not sufficiently good, the gas was refractionated, rejecting the first and last fractions, until the balancing pressures of the middle fractions were identical. This sample of gas was finally regarded as pure and was used for the first series of accurate comparisons with oxygen at two different pressures.

The obtaining of this pure propane formed one of the most difficult parts of the work, involving much labour and patience in the testing and refractionation of the various samples. [At this stage it was thought that vapour pressure measurements at the temperature of solid carbon dioxide and alcohol might furnish a further test of the purity of the gas. A number of measurements with different samples was made, but this method proved less sensitive than a comparison of balancing pressures. We found 105·8 mm. as the vapour pressure at −78·5°, which is lower than the value 130·5 mm. from the vapour-pressure measurement of Burrel and Robertson (*J. Amer. Chem. Soc.*, 1915, **37**, 2188).] The ratios obtained from this first series were not very consistent. This might have been due to impurities still remaining in the gas, most probably traces of unsaturated compounds, and it was decided to hydrogenate the gas and then purify it as before. Dr. Atack and Dr. McCormack kindly hydrogenated a sample of their original gas, over a promoted nickel catalyst at 300—350°. The resulting gas was condensed in a vessel surrounded with liquid air. One third was allowed to boil off, removing most of the ethane. The second fraction, about 4 l. of gas, was transferred to evacuated storage flasks. The

remaining third of the liquid was discarded, containing most of the heavier impurity butane. The hydrogenated gas was subjected to the same chemical purification as before except that it was passed and repassed through the purification train five times in all. It was then fractionated as previously and collected in two fractions. The third fraction was rejected.

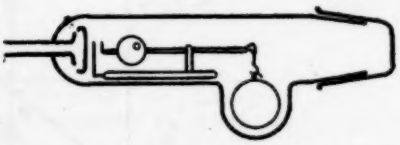
A second series of accurate comparisons with oxygen at two different pressures was obtained from the second fraction of this sample of propane. The results obtained were more consistent than those of the first series. The final calculation of the molecular weight of propane showed very good agreement between the two series, suggesting that gas of a very high standard of purity had been obtained.

Earlier, an attempt had been made to prepare propane from propyl cyanide and sodium by Timmermans's method (*J. Chim. physique*, 1920, **18**, 133). Only a small quantity of gas was obtained, insufficient for a series of experiments. On testing with the microbalance it was found to be too light, probably owing to the presence of unsaturated hydrocarbons. This method of preparation was therefore abandoned and the more profitable one detailed above used.

(b) *Oxygen.* The oxygen used as the standard for the comparisons was obtained from "AnalaR" potassium permanganate. Initially, air was expelled by evacuating, then heating slightly, and evacuating again. The oxygen was passed over solid potassium hydroxide to eliminate possible traces of carbon dioxide and then dried (P_2O_5). It was next bubbled through mercury to remove traces of ozone, and finally taken into the balance case through a long glass spiral cooled in liquid air. The oxygen was freshly prepared for each filling, and not stored.

Course of an Experiment.—Before making a filling with either gas, the whole apparatus was thoroughly evacuated. A Speedivac oil-pump was used until the pressure was about 0·002 mm., and the remaining traces of gas were removed with a charcoal tube cooled in liquid air. The pressure was tested by means of an accurate McLeod gauge until it registered practically zero. It was usually possible, with the charcoal tube, to reach a pressure of about 0·00008 mm. in about 20 minutes. It was necessary to leave the apparatus in a high vacuum overnight and then pump down again before interchanging the gases. If this was not done, particularly when the previous gas in the apparatus was propane, the pressure readings on the second gas showed a decided drift, presumably owing to slow release of gas adsorbed by the greased joints and the glass walls. This long period of high vacuum was more satisfactory in removing adsorbed gases than washing out with the gas before filling.

FIG. 4.



To obviate this adsorption, an alternative to Apiezon grease was sought. Finally, the original soda-glass balance case with two ground joints was replaced with a Pyrex case with one joint (Fig. 4). Also the connecting tubes were modified to reduce the number of taps. Edwards W.E.Wax No. 6 proved the most satisfactory for the balance-case joint, having little or no vapour pressure at 20° and being unaffected by the gases used. When the second series of propane measurements was made, these modifications to the apparatus helped to eliminate the delayed desorption of propane, and the lowering of the oxygen pressure was not so noticeable.

To ensure that the propane was free from air before taking it into the balance case it was liquefied in a small bulb immersed in liquid air, which was close to the balance case, and then thoroughly evacuated first with the Speedivac pump and finally with the cooled charcoal tube. The pressure was tested on the McLeod gauge and could easily be lowered to 0·0001 mm. The liquid was then allowed to evaporate and the gas taken into the balance case and manometer very slowly until the balance began to swing freely. The balance was adjusted roughly by means of the main mercury reservoir so that the fixed pointer and the pointer attached to the balance were in a horizontal line. The points were viewed through a telescope with a micrometer eyepiece through a glass window in the side of the tank.

Before making the final adjustment, the tube connecting the mercury reservoir to the manometer (Fig. 3) was clipped to prevent alterations in the barometric pressure from affecting the reading. The final adjustment was made with the pressure adjuster. After filling, it was necessary to leave the apparatus for 3—4 hours for steady temperature conditions to be reached. The balance was then set accurately to the zero point, and the pressure read off on the manometer, each reading being taken three times, and the mean determined. The temperatures of the balance case and manometer tank were noted. After about an interval of an hour, the mercury in the manometer was lowered by a few mm. by means of the main reservoir and then raised again. The balance was reset, and the pressure and temperatures recorded a second time. About five sets of readings were taken in this manner.

After evacuation of the apparatus as described above, the freshly prepared oxygen was taken into the apparatus to the approximate balancing pressure and readings taken as for propane.

Table I shows a typical series of results for two consecutive fillings of propane and oxygen, respectively, taken from Series II.

Corrections.—Various corrections have to be applied to the results before the final figure is obtained. The thermometers used in the manometer tank and tank surrounding the balance case were compared with an N.P.L. Standard thermometer of 20—30° range, and a list of corrections drawn up to 0·01°.

The glass Cowlishaw scale used to measure the pressure was compared with a Standard Société Genevoise Scale, and a correction curve drawn.

The mercury column was corrected to 0°, latitude Leeds. The balance-case temperature was corrected in each case to 20·76°, that being the mean temperature of the experiments. It was not considered advisable to carry out the necessarily large extrapolation involved in reducing all balancing temperatures to zero.

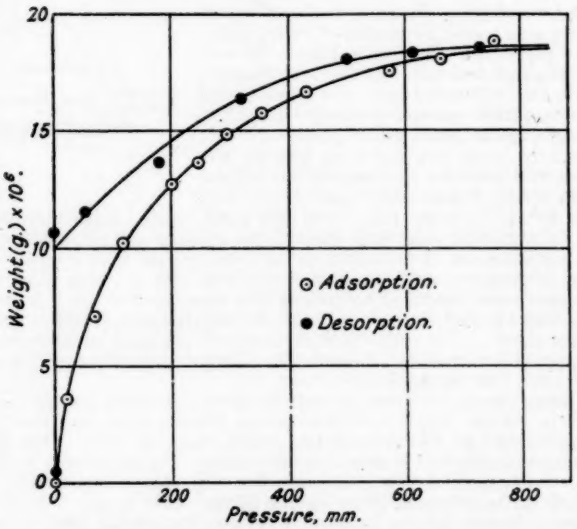
Finally a Rayleigh correction was made for change of buoyancy due to the slight contraction when propane is replaced by oxygen. The contraction of the bulb, measured on a bulb of similar volume and weight, was found to be 3 cu. mm. per 760 mm. pressure.

Results.—Propane and oxygen were put into the balance case, alternately. Several readings were

TABLE I.

Corrected scale readings.		Pressure, mm., Hg.	Corrected manometer temp., °C.	Corrected balance temp., °C.	Pressure, corrected to 0° c., mm.	Pressure, corrected to balance temp., 20·76°, mm.	Mean pressure, mm.	Final pressure, mm. Buoyancy correction added.
444·47	947·33	502·86	20·90	20·764	501·05	501·05		
444·26	947·14	502·88	20·91	20·766	501·07	501·05		
444·11	946·99	502·88	20·90	20·761	501·07	501·07	501·06	501·12
444·16	947·04	502·88	20·90	20·766	501·07	501·05		
444·23	947·10	502·87	20·90	20·759	501·06	501·06		
225·90	926·33	700·43	20·92	20·771	697·92	697·90		
225·83	926·27	700·44	20·92	20·759	697·93	697·93		
225·72	926·18	700·46	20·92	20·763	697·95	697·95	697·92	697·94
225·90	926·36	700·46	20·91	20·769	697·95	697·93		
225·88	926·32	700·44	20·91	20·769	697·93	697·91		

FIG. 5.



Weight of propane adsorbed on surface of 123 *sq. cm. for pressure range* 0—800 *mm.*

taken with each filling, taking about a day and a half. Individual measurements agreed within 0·03 mm. The results, recorded in Tables II and III, are a summary of all the measurements taken, after all corrections have been applied. Each pressure reading is the mean of about five readings. The measurements in each series were consecutive. All the results obtained are included.

Adsorption.—To find out to what extent this effect could impair the accuracy of our results, the adsorption of propane on blown surfaces of vitreous silica was measured independently by direct weighing, using another microbalance designed for this purpose. In Fig. 5, the total weight adsorbed is plotted against pressure.

From these results the weights of propane adsorbed on the surface of the buoyancy bulb were calculated, for pressures of 501 and 254 mm., as $2·8 \times 10^{-4}$ g. and $2·3 \times 10^{-4}$ g., respectively. These figures would give a correction to the observed balancing pressures of 0·13 and 0·11 mm., which would increase the molecular weight from 44·098 to 44·124, corresponding to an increase in the atomic weight of carbon from 12·011 to 12·020. Hence had the balance been uncompensated the results obtained would have been too high by this amount. Actually, since the surface areas on the two sides of the balance beam were within 10% of equality, we regard our results as free from adsorption error within the limits of accuracy of our measurements.

The work mentioned on the adsorption of propane has not yet been published. The values obtained seem to us very large in comparison with corresponding concordant values obtained with sulphur dioxide in two investigations in this laboratory. It seems unlikely that the adsorption of propane on blown-silica surfaces is so much greater than that of sulphur dioxide. Although great care was taken to ensure clean surfaces, it is possible that these were contaminated by adsorbed Apiezon-grease vapour from the ground joints in the adsorption-balance case and that the values obtained are for adsorption on a grease film. Since, however, the density balance was equally liable to grease-vapour contamination in the first series, we have used the high values in the above calculation to obtain a measure of the maximum possible error.

TABLE II.

Series I.

Low pressure. Mean corrected pressure, mm. Hg. O_2	C_3H_8	Ratio O_2/C_3H_8.	High pressure. Mean corrected pressure, mm. Hg. O_2	C_3H_8	Ratio O_2/C_3H_8.
352·58	—	1·38538	—	478·95	1·39165
—	254·50	1·38534	666·53	—	1·39165
352·57	—	1·38534	—	478·95	1·39167
—	254·50	1·38503	666·54	—	1·39208
352·49	—	1·38492	—	478·81	1·39170
—	254·52		666·36	—	1·39150
			—	478·88	1·39137
			666·30	—	
Mean values: 352·540	254·504	1·38520 ±0·00008	666·451	478·890	1·39166 ±0·00005

Cawood and Patterson (*loc. cit.*) derived the expression

$$p_1/p_2 = [M_2(1 - A_1p_1)]/[M_1(1 - A_2p_2)] = r$$

where r is the ratio of the two pressures, and A is the compressibility as defined by $p_1V_1/p_0V_0 = 1 - A$.

This gives a linear plot of r against p, and, extrapolating to zero pressure, we have limiting ratio, $r_0 = M_2/M_1$.

Since M_1 = molecular weight of oxygen = 32, $r_0 = 1{\cdot}37794$, the molecular weight of $C_3H_8 = 44{\cdot}094$. Assuming H = 1·0080, the atomic weight of carbon = 12·010.

TABLE III.

Series II.

Low pressure. Mean corrected pressure, mm. Hg. O_2	C_3H_8	Ratio O_2/C_3H_8.	High pressure. Mean corrected pressure, mm. Hg. O_2	C_3H_8	Ratio O_2/C_3H_8.
—	254·49	1·38540	697·95	—	1·39275
352·57	—	1·38551	—	501·13	1·39273
—	254·47	1·38543	697·94	—	1·39276
352·55	—	1·38548	—	501·12	1·39276
—	254·46	1·38560	697·94	—	1·39243
352·58	—	1·38533	—	501·24	1·39265
—	254·51	1·38537	698·05	—	1·39267
352·59	—		—	501·23	
Mean values: 352·570	254·481	1·38545 ±0·00002	697·973	501·173	1·39268 ±0·00002

Limiting ratio, r_0, = 1·37807 ± 0·00006.
Molecular weight of C_3H_8 = 44·098 ± 0·002.
Assuming H = 1·0080, the atomic weight of carbon = 12·011 ± 0·001.

DISCUSSION.

From the results obtained in the two series of measurements it is evident that a linear extrapolation to zero pressure, *i.e.*, extrapolation over a range of 352 mm. of oxygen pressure gives two values (44·094 and 44·098 ± 0·002) for the molecular weight of propane which are in close accord and differ only slightly from the molecular weight calculated from International atomic weight values, *i.e.*, 44·094.

In view of the slight uncertainty in the third decimal place of the atomic weight of carbon,

due to a variation in the C_{12}/C_{13} ratio in carbon from different sources (Nier, *J. Amer. Chem. Soc.*, 1939, **61**, 697), the agreement of our results (12·010 and 12·011 ± 0·001) with the standard is as close as can be hoped for.

It is thus concluded that a strictly linear extrapolation is, for this gas, fully justified and that any curvature in the *PV–P* isothermal at 20·76° for propane, a gas with a critical temperature of 95°, is beyond the limits of accuracy of our measurements.

Strong support for this conclusion is afforded by an independent research on the compressibility of propane carried out in these laboratories by Dr. G. A. Bottomley. A full account of this work will be published shortly, and only his final results will be quoted. Using a specially-designed differential-compressibility apparatus (Thesis, Leeds, 1946), which by measurements with nitrogen and carbon monoxide was proved to give high accuracy, he determined the *PV–P* isothermal for propane at 22·02° from 800 to 100 mm. pressure. Two sets of measurements were made of 6 and 5 points, respectively. Strict mathematical treatment by the method of least squares showed the deviation from a straight line to be indetectable and within the limits of the errors of experiment.

The mean value found by Dr. Bottomley for the coefficient of deviation from Boyle's law for propane at 22·02° is $A_{C_3H_8} = 0{\cdot}016814$ per atmosphere.

To correct the value from 22·02° to 20·76°, the temperature at which the microbalance ratios were measured, a small correction is necessary. We have used for this correction the values found for A for propane at 0° and 50° by Jessen and Lightfoot (*Ind. Eng. Chem.*, 1938, **30**, 312) and interpolated these assuming a linear relation between A and $1/T$. The corrected value for 20·76° then becomes 0·016991.

Using the same apparatus we have determined the corresponding coefficient for oxygen at 22·02° as $A_{O_2} = 0{\cdot}00068$ per atmosphere. Using this latter coefficient we can calculate from our micro-balance ratios the compressibility coefficient of propane by means of the formula (Cawood and Patterson, *loc. cit.*, p. 99),

$$A = \frac{r''(1 - A_1p_1') - r'(1 - A_1p_1'')}{r''(1 - A_1p_1')p_2'' - r'(1 - A_1p_1'')p_2'}$$

where r' and r'' are microbalance ratios, p_1' and p_1'' are oxygen pressures, p_2' and p_2'' are corresponding propane pressures, and A_1 is the compressibility of oxygen.

Thus, we find for Series I, $A = 0{\cdot}016584$, and for Series II, $A = 0{\cdot}016832$. Series II, which we regard as the soundest experimentally, gives a value for the compressibility which agrees satisfactorily with the above value found by Dr. Bottomley. Series I gives a distinctly lower value and exemplifies what has been noticed before, that microbalance ratios when extrapolated to zero pressure may give a correct limiting value, but an incorrect slope (Patterson and Cawood, *loc. cit.*, p. 100).

Using Dr. Bottomley's corrected value for the compressibility and our value for oxygen, we can now calculate values for the molecular weight of propane from each pressure ratio in Series II (Table III) from the expression on p. 1751. These are low-pressure ratio 44·096, high-pressure ratio 44·094, and mean 44·095. We have then, for the molecular weight of propane, the following:

	Mol. wt.	At. wt. of carbon (H = 1·0080).
Microbalance, series I	44·094	12·010
,, ,, II	44·098	12·011
Compressibility, series II	44·095	12·010
Mean	44·095 (7)	12·010 (6) *

* Calc. from mean mol. wt.

These figures appear to us to be the most probable from our data.

We wish to express our thanks to the Department of Scientific and Industrial Research for an assistantship to one of us (F. L. C.) and to Imperial Chemical Industries Ltd. for the help of another (D. S. M.). The third author thanks the Leverhulme Trustees for financial support during the earlier part of the work. One of us (F. L. C.) also thanks the Patronato de la Universidad de Santiago de Compostela for a scholarship covering the earlier part of the work.

THE UNIVERSITY, LEEDS. [*Received, December 15th*, 1948.]

374. *The Preparation of Symmetrical Aromatic Triamines and Triisocyanates.*

By J. E. Gill, R. MacGillivray, and J. Munro.

Catalytic reduction of symmetrical aromatic trinitro-compounds in ethyl acetate solution, using Raney nickel as catalyst, has been shown to be a convenient method for the preparation of symmetrical aromatic triamines. The corresponding triisocyanates, triurethanes, and triureido-derivatives have also been prepared.

The preparation and isolation of *s*-aromatic triamines have in the past proved difficult, and before the present work the only amines of this type reported have been 2 : 4 : 6-triaminotoluene (Hein and Wagner, *Ber.*, 1935, **68**, 856) and 2 : 4 : 6-triaminoanisole (Damschroder and Shriner, *J. Amer. Chem. Soc.*, 1937, **59**, 931). These workers had trouble in isolating the amines, which they prepared by catalytic reduction of the corresponding nitro-compounds in ethyl alcohol solution, and all their manipulations had to be carried out in an oxygen-free atmosphere.

Aliphatic alcohols are not good media for the reduction of polynitro-compounds as they are poor solvents for the nitro-compounds but, when diluted with the water formed during reduction, they are very active solvents for the amines produced, and isolation is correspondingly difficult. Ethyl acetate is employed as solvent in the following hydrogenation method, with Raney nickel as catalyst, and a number of new *s*-triamines has been isolated without difficulty and in good yield. The success of ethyl acetate as solvent depends on (*a*) its good solvent power for aromatic nitro-compounds, (*b*) its relatively poor solvent power for the corresponding amines which therefore crystallise readily at the end of the reaction, and (*c*) the fact that the water formed during reduction of the nitro-groups is miscible with this solvent at the concentrations used. [The solubility of water in ethyl acetate is 4—5% between 50° and 60° (Merriman, *J.*, 1913, 1774).] Methyl acetate may also be used, but the miscibility of the higher homologues with water is too low to permit them to be used successfully. Hydrogen pressures around 40 lbs. per sq. in. have given the optimum rates of reduction, but reaction can be effected even at atmospheric pressure if the solution is heated during reduction. The method is also applicable to the preparation of mono- and di-amines.

The reaction of phosgene with the hydrochlorides of these amines suspended in a phosgene-inert solvent appears to be a general method for the preparation of symmetrical aromatic triisocyanates.

Experimental.

s-Aromatic Triamines.—An ethyl acetate solution of the *s*-trinitro-compound (5% concentration or 3% in the case of *s*-trinitrobenzene) is shaken with hydrogen at about 40 lbs. per sq. in. initial pressure and Raney nickel catalyst (15% of the weight of the nitro-compound) (*Org. Synth.*, 1941, **21**, 15). The temperature is allowed to rise unchecked. At the end of the reduction the solution should be colourless or faintly pink. The reaction time varies from 30 to 80 minutes depending on the quantity of materials used and the efficiency of shaking. The amine is obtained in crystalline form by filtering off the spent catalyst and leaving the ethyl acetate solution to cool.

The properties of several of these triamines are indicated in Table I.

Table I.

s-Triamine of	M. p.	Yield, %	Analyses, %. Formula.	Found: C.	H.	N.	Requires: C.	H.	N.	Benzoyl derivative, m. p.
Benzene	84° * 108—112 †	76	$C_6H_9N_3,H_2O$	51·08	7·66	29·15	51·06	7·80	29·79	356—357°
Toluene	121—122	60	—	—	—	—	—	—	—	—
Ethylbenzene	73—74 *	60	$C_9H_{13}N_3,H_2O$	57·10	8·83	24·80	56·81	8·87	24·84	292—293
Chlorobenzene	97	60	$C_6H_8N_3Cl$	45·81 (Cl, 22·19)	5·33	26·20	45·71 (Cl, 22·54)	5·08	26·66	261
Anisole	117—118	80	—	—	—	—	—	—	—	232
Phenetole	124—125	94	$C_9H_{13}ON_3$	57·40	8·15	24·70	57·49	7·79	25·15	206—207
Phenyl isobutyl ether	b. p. 184—185/2 mm.	80	$C_{10}H_{17}ON_3$	61·00	8·42	21·50	61·54	8·72	21·54	235—236
Diphenyl ether	145	74	$C_{12}H_{13}ON_3$	67·06	6·04	20·23	66·99	6·05	19·54	258—259
Phenylethanol	131—132	55	$C_9H_{13}ON_3$	57·10	7·74	25·80	57·49	7·79	25·15	293—294
Phenylethyl acetate	106—107	71	$C_{10}H_{15}O_2N_3$	—	—	19·60	—	—	20·10	—

* Hydrated. † Anhydrous.

All the amines have been obtained as colourless needles which darken slowly on being left in air, but they have been kept for periods of up to 2 months without appreciable change in colour when stored under vacuum over phosphoric oxide. Chemically they are all very similar, being very soluble in water and alcohols and in mineral acids with salt formation. They are less soluble in the lower saturated aliphatic esters and only slightly soluble in hydrocarbon solvents. They are not soluble in ether and petroleum. The benzoyl derivatives are prepared with benzoyl chloride and aqueous alkali.

The hydrochlorides can be prepared in quantitative yields by saturating with dry hydrogen chloride the ethyl acetate solutions obtained on reduction of the nitro-compounds.

Stable amines could not be prepared by reduction of the following compounds under the above conditions; picric acid, *s*-trinitrobenzoic acid, methyl *s*-trinitrobenzoate, *s*-trinitroaniline, *s*-trinitroacetanilide, *s*-trinitrophenylmethylnitroamine or 1-bromo-, 1-iodo-, and 1-fluoro-*s*-trinitrobenzenes.

s-Aromatic Triisocyanates.—Carbonyl chloride is passed into a suspension of the appropriate amine hydrochloride (1 part) in chlorobenzene (10 parts) under anhydrous conditions and the temperature is raised to 110—120° and maintained there until the solid passes into solution as the tri*iso*cyanate and hydrogen chloride ceases to be liberated. At the end of the reaction excess of carbonyl chloride is removed by blowing a stream of dry nitrogen through the mixture, and the solution is filtered, if necessary, from any insoluble material. The solvent is then removed under reduced pressure, and the tri*iso*cyanate purified by distillation under reduced pressure.

TABLE II.

s-Tri*iso*-cyanate of	M. p.	Yield, %	Formula.	Analyses, %. Found: C.	H.	N.	Required: C.	H.	N.	Urethane, m. p.	Urea, m. p.
Benzene	84—85°	50	$C_9H_3O_3N_3$	53·61	1·50	21·00	53·73	1·49	20·89	191—192°	>350°
Toluene	78—79	73	$C_{10}H_5O_3N_3$	55·80	2·42	19·90	55·82	2·33	19·54	199—200	306—307
Ethylbenzene	48—49	78	$C_{11}H_7O_3N_3$	57·70	3·20	18·29	57·65	3·06	18·34	225—226	289—291
Chlorobenzene	93·5—94·5	67	$C_9H_2O_3N_3Cl$	46·20	1·10	18·00	45·85	0·85	17·83	154—155	288—289
Anisole	83—83·5	78	$C_{10}H_5O_4N_3$	51·90	2·24	18·22	51·95	2·16	18·18	114—115	283—284
Phenetole	49—49·5	71	$C_{11}H_7O_4N_3$	53·59	3·15	16·94	53·88	2·85	17·14	134—135	263—264
Diphenyl ether	78—78·5	61	$C_{15}H_7O_4N_3$	61·99	2·41	14·46	61·44	2·39	14·33	liquid	271—272

All the tri*iso*cyanates examined are fairly low-melting solids which crystallise as colourless needles. They react readily with moisture and have to be stored under anhydrous conditions. Aromatic hydrocarbons and chlorinated hydrocarbons are good solvents and the tri*iso*cyanates may be recrystallised from them.

The triurethanes are readily prepared by dissolving the tri*iso*cyanates in hot ethyl alcohol and allowing the solutions to cool. The triureido-compounds are obtained by adding ether containing excess of dry ammonia gas to ethereal solutions of the tri*iso*cyanates. They can be recrystallised from water. Table II indicates the properties of several of these compounds.

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375. *The Fission of the Thioether Linkage in Certain β-Sulphonyl-sulphides.*

By A. H. FORD-MOORE, R. A. PETERS, and R. W. WAKELIN.

Di-[2-(2′-amino-2′-carboxyethylthio)ethyl] sulphone (II) and *S*-2′-phenylsulphonylethylcysteine (I) undergo fission of the thioether group on treatment with silver salts at pH 7·8—8. Cysteine is formed in both cases. With (I), phenyl vinyl sulphone has also been identified.

s.-2′-Phenylsulphonylethylthioacetic acid (VI) also undergoes fission under similar conditions, but *o*-2-phenylsulphonylethylthiobenzoic acid (V) does not.

DIVINYL sulphone, first prepared by (the late) E. Walker (Ministry of Supply Report, 1926; *J.*, 1931, 1914), is a very reactive substance, and Alexander and McCombie (*J.*, 1931, 1913) have shown that compounds containing hydroxy-, mercapto-, or amino-groups react with it very readily, a hydrogen atom adding to the α-carbon atom and the rest of the molecule to the β-carbon atom. Reaction with a mercapto-group is particularly rapid, and, when divinyl sulphone reacts with a substance such as cysteine, that contains both mercapto- and amino-groups, combination occurs predominantly with the former. This reactivity extends to those compounds, like *phenyl vinyl sulphone* (IV), that only contain one vinyl group.

It has now been shown that the reaction between thiols and compounds containing the group

·SO_2·$CH{:}CH_2$ is, under conditions approximating to the biological, reversible. Peters and Wakelin (Ministry of Supply Report, No. 39, 1941; *Biochem. J.*, 1947, **41**, 555) have found that the thioether linkage in the *product* (II) of reaction of cysteine with divinyl sulphone and in that (I) from cysteine and phenyl vinyl sulphone can be split by treatment, at slightly alkaline pH, with silver salts, since the cysteine fragment from (II) can be isolated as its oxidation product,

$Ph{\cdot}SO_2{\cdot}CH_2{\cdot}CH_2{\cdot}S{\cdot}CH_2{\cdot}CH(NH_2){\cdot}CO_2H$ (I.) $\qquad$ $SO_2[CH_2{\cdot}CH_2{\cdot}S{\cdot}CH_2{\cdot}CH(NH_2){\cdot}CO_2H]_2$ (II.)

cystine. The sulphone fragment from (II) does not readily lend itself to isolation and characterisation; so in order to simplify the problem, attention was turned to a compound such as (I), which only contains one cysteinyl group and which also contains a readily identified sulphone fragment. On fission, (I) should give cysteine (or its oxidation product, cystine) and either phenyl 2-hydroxyethyl sulphone (III) or phenyl vinyl sulphone (IV):

$$(I) \rightarrow Ph{\cdot}SO_2{\cdot}CH_2{\cdot}CH_2{\cdot}OH \text{ (III.)} + \text{cysteine} \quad \ldots\ldots\ldots (a)$$

$$(I) \rightarrow Ph{\cdot}SO_2{\cdot}CH{:}CH_2 \text{ (IV.)} + H_2O + \text{cysteine} \quad \ldots\ldots\ldots (b)$$

For identification of the sulphone fragment, derivatives of (III) and (IV) have been prepared. (III) can be characterised as its p-*nitrobenzoate*. (IV) is itself a crystalline solid but can be further characterised as its p-*tolylthio*-derivative by treatment with *p*-thiocresol.

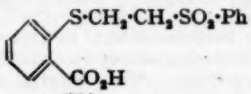
(I) was prepared from thiophenol as follows:

$$Ph{\cdot}SH \xrightarrow[NaOH]{Cl{\cdot}[CH_2]_2{\cdot}OH} Ph{\cdot}S{\cdot}CH_2{\cdot}CH_2{\cdot}OH \text{ (VII.)} \xrightarrow{SOCl_2} Ph{\cdot}S{\cdot}CH_2{\cdot}CH_2Cl \text{ (VIII.)} \xrightarrow{H_2O_2} Ph{\cdot}SO_2{\cdot}CH_2{\cdot}CH_2Cl \text{ (IX.)}$$

$$\xrightarrow{NEt_3} (IV) \xrightarrow[NaHCO_3]{Cysteine} (I)$$

On treatment with silver salts at the appropriate pH, (I) breaks down according to scheme (*b*), the cysteine appearing as cystine and the sulphone fragment as (IV).

In an attempt to obtain a more rigid proof of the course of the reaction, the condensation product of (IV) with *o*-mercaptobenzoic acid, namely o-2-*phenylsulphonylethylthiobenzoic acid* (V), was prepared. It was thought that, if this compound could be split on "silver treatment," the thio-fragment would appear either as *o*-mercaptobenzoic acid or as its oxidation product, the corresponding disulphide; both these two compounds are crystalline solids of definite melting point. Unfortunately, (V) did not respond to "silver treatment." This is in all probability due to the fact that fission is preceded by the formation of a silver complex at the thioether atom. (V) is less likely to form such a complex than is a purely alkyl sulphide. That fission is not due to the presence of an amino-group was demonstrated by preparing 2-



(V.) $\qquad$ $Ph{\cdot}SO_2{\cdot}CH_2{\cdot}CH_2{\cdot}S{\cdot}CH_2{\cdot}CO_2H$ (VI.)

phenylsulphonylethylthioacetic acid (VI) and showing that this compound undergoes fission in a similar manner to (I) and (II), since it gives the nitroprusside reaction on "silver treatment."

Experimental.

Phenyl 2-hydroxyethyl sulphide (VII) was prepared from ethylene chlorohydrin (41 g., 33 c.c.) and a solution of thiophenol (55 g.) in 20% aqueous sodium hydroxide (120 c.c.), the reaction being completed by heating on a steam-bath for 1 hour. After cooling, the mixture was extracted with chloroform, the chloroform layer separated, and the solvent distilled off. The residue was distilled and a fraction collected at 135°/8 mm. (141°/11 mm.) (Nenitzescu and Scarlatescu, *Ber.*, 1935, *B*, **68**, 587, give b. p. 119—120°/4 mm.) (yield, 61·5 g., 80%); the product had d_{15}^{24} 1·1145, n_D^{22} 1·5870, and was characterised as p-*nitrobenzoate*, m. p. 57—58° (from methanol) (Found: C, 59·6; H, 4·2. $C_{15}H_{13}O_4NS$ requires C, 59·4; H, 4·3%).

Phenyl 2-chloroethyl sulphide (VIII), prepared from thionyl chloride (45 c.c.) and (VII) (55 g.) in dry chloroform (150 c.c.), boiled at 107°/7 mm. (123°/14 mm.) (yield, 56 g.) and had $d_{15}^{22\cdot5}$ 1·1820 (Dawson, *J. Amer. Chem. Soc.*, 1933, **55**, 2070, gives b. p. 88—89°/0·637 mm., *d* 1·1769) (Found: Cl, 20·85. Calc. for C_8H_9ClS: Cl, 20·5%). Although not so active as mustard gas, this substance is strongly vesicant, and care should be exercised in handling it; contaminated apparatus may be rendered harmless by treatment with concentrated nitric acid.

Phenyl 2-chloroethyl sulphone (IX) was prepared by oxidising (VIII) (8·5 g.) with 30% hydrogen peroxide (15 c.c.) in glacial acetic acid (35 c.c.), the reaction being completed by boiling the mixture gently under reflux for 0·5 hour. The product was isolated by pouring the mixture into water and purified by crystallising from ethanol (yield, pure, 8 g., 78·5%); m. p. 55° (Kretov and Toropova, *J. Gen. Chem. U.S.S.R.*, 1937, **7**, 2009, give m. p. 52°) (Found: Cl, 17·6. Calc. for $C_8H_9O_2ClS$: Cl, 17·3%).

Phenyl 2-hydroxyethyl sulphone (III) was prepared by oxidising (VII) with a slight excess of 30% hydrogen peroxide in acetic acid. It did not solidify but distilled without decomposition at 177°/2 mm. and had n_D^{11} 1·5573. It was characterised as its *p-nitrobenzoate*, m. p. 151—152° (from acetic acid) (Found: C, 53·4; H, 3·9. $C_{15}H_{13}O_6NS$ requires C, 53·7; H, 3·9%). The same ester was obtained by the oxidation of the *p*-nitrobenzoate of (VII) with hydrogen peroxide in acetic acid.

Phenyl vinyl sulphone (IV) was prepared by treating (IX) (10 g.) in benzene (100 c.c.) with triethylamine (5 g., 7 c.c.) and setting the mixture aside overnight. After the triethylamine hydrochloride had been removed, the benzene was distilled off and the residue treated with light petroleum (b. p. 40—60°). The product solidified and was recrystallised from benzene–light petroleum (b. p. 40—60°). The yield of pure product melting at 68·5° was 6·5 g. (79%) (Found: C, 57·1; H, 5·0. $C_8H_8O_2S$ requires C, 57·1; H, 4·8%).

p-*Tolyl 2-Phenylsulphonylethyl Sulphide*.—(*a*) Thio-*p*-cresol (1·5 g.) and (IV) (2 g.) were warmed with a trace of triethylamine. Heat was evolved and, on cooling, the *sulphide* solidified. It was crystallised from ethanol and melted at 95—96° (Found: C, 61·3; H, 5·2. $C_{15}H_{16}O_2S_2$ requires C, 61·6; H, 5·5%).

(*b*) Thio-*p*-cresol (3 g.), dissolved in a solution of sodium (0·8 g.) in ethanol (30 c.c.), was treated with (IX) (5 g.), and the mixture heated on a steam-bath for 1 hour. The mixture was filtered hot; when cooled, the filtrate deposited crystals of the sulphide, which after recrystallisation from ethanol melted at 95—96°, not altered on admixture with the product from (*a*).

S-2-*Phenylsulphonylethylcysteine* (I).—Cysteine hydrochloride (1·5 g.) was added to (IV) (1·7 g.) in 5% aqueous sodium hydrogen carbonate (25 c.c.) at 40°. The mixture was heated on a steam-bath for 2 hours and then cooled, and any unchanged (IV) extracted with chloroform. The *cysteine* derivative (2·5 g., 86·5%) separated when the solution was kept. It was recrystallised from water and melted with decomposition at 200—203° (Found: C, 45·3; H, 5·2. $C_{11}H_{13}O_4NS_2$ requires C, 45·6; H, 5·2%).

o-2-*Phenylsulphonylethylthiobenzoic Acid* (V).—*o*-Mercaptobenzoic acid (3·7 g.), (IV) (4 g.), benzene (30 c.c.), and a trace of triethylamine were heated under reflux for 0·5 hour. When it had cooled, the benzene solution was extracted with aqueous sodium carbonate, and the latter separated and acidified with hydrochloric acid. The separated *acid* was filtered off and crystallised from ethanol; m. p. 203° (Found: C, 56·3; H, 4·7. $C_{15}H_{14}O_4S_2$ requires C, 56·7; H, 4·7%).

2-*Phenylsulphonylethylthioacetic Acid* (VI).—Equimolar parts of (IV) and 90% thioglycollic acid were heated on a steam-bath for 4 hours with a trace of triethylamine. The product was treated with an aqueous suspension of barium carbonate and filtered. The filtrate, on acidification with hydrochloric acid, deposited an oily *acid* which rapidly solidified. It melted at 84° after crystallisation from benzene (Found: C, 46·3; H, 4·75. $C_{10}H_{12}O_4S_2$ requires C, 46·45; H, 4·5%).

Divinyl Sulphone.—2 : 2′-Dichlorodiethyl sulphone (100 g.; m. p. 57°; cf. Helfrich and Reid, *J. Amer. Chem. Soc.*, 1920, **42**, 1208), precipitated calcium carbonate (55 g.) and water (500 c.c.) were heated in a three-necked flask equipped with a sealed stirrer, a thermometer (bulb in liquid), and a reflux condenser, and set in a water-bath. After the mixture had been heated at 85—90° for about 4 hours, the reaction was complete. Some polymeric material was filtered off through glass wool, and the filtrate extracted with benzene in a continuous extractor for 2 hours. The extract was dried (anhydrous $MgSO_4$), and the benzene distilled off. The residue was distilled, a fraction being collected at 123—125°/18 mm. (98—100°/7 mm.) (Alexander and McCombie, *loc. cit.*, give b. p. 120—121°/18 mm.; their method is less convenient than ours for large quantities. Cf. also Levin, *J. pr. Chem.*, 1930, **127**, 77). The yield was 47—53 g. (79—85%). When cooled in "dry ice" and acetone, the sulphone froze at −16°.

The crude sulphone, obtained by oxidising an appropriate amount of mustard gas with hydrogen peroxide (2·5 moles) in acetic acid, may be used with practically no diminution in yield. Sodium hydrogen carbonate may be employed in place of calcium carbonate but, in this case the reaction temperature must be kept between 40° and 45° during the hydrolysis and any free alkali at the end of the reaction neutralised with hydrochloric acid before benzene extraction. The material may be stabilised by the addition of triethylamine (0·05%) and storage in a cool, dark place.

Di-[2-(2′-*amino-2′-carboxyethylthio*)*ethyl*] *Sulphone* (II).—A solution of divinyl sulphone in excess of 5% aqueous sodium hydrogen carbonate at 38° was treated with two molar equivalents of cysteine hydrochloride. Precipitation of the *biscysteine* derivative started almost at once and was complete in about 5 minutes. It was filtered off and crystallised from water (in which it was rather sparingly soluble) in minute, hair-like needles, melting with decomposition at 251—252° (Found: C, 33·2; H, 5·7. $C_{10}H_{20}O_6N_2S_3$ requires C, 33·3; H, 5·6%).

Divinyl sulphone can be conveniently determined by precipitation as the above compound. An aqueous solution containing about 0·15 g. of the sulphone is treated with 50 c.c. of 3% sodium hydrogen carbonate solution, and cysteine hydrochloride (not less than 0·4 g. per 0·15 g. of sulphone) in a little water is added. After 15 minutes the precipitate is collected on a weighed Gooch crucible, washed with a little ice-water, dried at 100°, and weighed. 0·234 Mg. is added to this weight for each c.c. of filtrate plus washings. 1 G. of condensation product corresponds to 118/360 g. of divinyl sulphone.

Fission of (II) *on Silver Treatment*.—500 Mg. of (II) were treated with 10 c.c. of 10% silver nitrate and adjusted to pH 3·0 with 4N-hydrochloric acid. After the mixture had been centrifuged, the filtrate still contained unchanged (II) [strong nitroprusside reaction on addition of silver nitrate (2 c.c.) and subsequently sodium hydroxide]. After the mixture had been re-adjusted to pH 3·0, the combined precipitates were washed with dilute hydrochloric acid and extracted with a solution of sodium iodide (2 g.) with the addition of hydrochloric acid to pH 3·0. Nitroprusside reactions on the centrifugate indicated the liberation of cysteine. The combined cysteine-containing extracts were evaporated to dryness *in vacuo* with the addition of acid to pH 3·0. Aqueous ammonia (*d* 0·880; 0·4 c.c.) was added and, after shaking, the whole was allowed to oxidise at room temperature for 24 hours. The remaining

ammonia was removed *in vacuo*, and the residue dissolved in dilute hydrochloric acid, the small amount of insoluble material being removed by micro-filtration. The cystine was precipitated in crude form by adjusting the pH to 4·0 in successive fractions. The first fractions required redissolution in 0·1N-hydrochloric acid with slight warming and further filtration before typical hexagonal plates of cystine (26 mg.) could be obtained. Fission was not complete, as *ca.* 300 mg. of unchanged (II) were recovered from the filtrate from the silver precipitate.

Isolation of (IV) *from the Silver Treatment of* (I).—(I) (200 mg.) was treated as described for (II). The aqueous filtrate at pH 3·0 from the silver–cysteine complex after alkali treatment was evaporated to dryness *in vacuo* at <50°, traces of sodium hydroxide being added during the concentration to prevent a fall in pH. The residue was extracted with chloroform, and the latter removed *in vacuo*, leaving an oil that slowly crystallised. On re-extraction and centrifugation, 62 mg. of crystals, m. p. 66·5° [67° on admixture with an authentic specimen of (IV)], were obtained.

The identity of the sulphone fragment was confirmed by converting 45 mg. of the recovered compound into its *p*-tolylthio-derivative by warming with *p*-thiocresol (37 mg.) and a trace of triethylamine. The product, after crystallisation from light petroleum and then from ethanol, melted at 95°, not altered on admixture with an authentic specimen.

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376. *The Constitution of Egg Plum Gum. Part III. The Hydrolysis Products obtained from the Methylated Gum.*

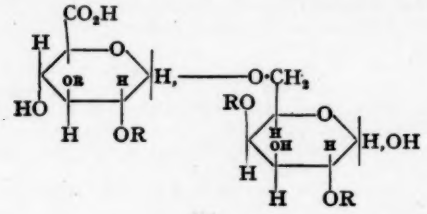
By F. Brown, E. L. Hirst, and J. K. N. Jones.

Methylated egg plum gum has been hydrolysed and the following sugars identified amongst the products of hydrolysis: (*a*) 2 : 3 : 4-trimethyl D-xylose, (*b*) 2 : 3 : 5-trimethyl, 2 : 5-dimethyl, and 2-methyl L-arabinose, (*c*) 2 : 4 : 6-trimethyl and 2 : 4-dimethyl D-galactose, and (*d*) 2 : 3-dimethyl D-glucuronic acid. The bearing of these results on the constitution of the gum is discussed.

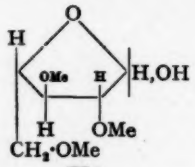
The products of the hydrolysis of egg plum gum have been identified as D-xylose, L-arabinose, D-galactose, and D-glucuronic acid in the approximate proportions 1 : 3 : 3 : 1 (Part I, *J.*, 1947, 1064). Hydrolysis of the gum with dilute acid results in the removal of the labile L-arabinose and D-xylose residues leaving a more resistant portion of the polysaccharide designated the degraded gum. This material on methylation, followed by hydrolysis, gives a mixture of methylated derivatives of D-galactose and D-glucuronic acid, identified as 2 : 3 : 4 : 6-tetramethyl, 2 : 4 : 6-trimethyl, 2 : 3 : 4-trimethyl, and 2 : 4-dimethyl D-galactose, and 2 : 3-dimethyl D-glucuronic acid (Hirst and Jones, *J.*, 1948, 120). The degraded gum on further hydrolysis yields D-galactose and an aldobionic acid consisting of a D-glucuronic acid residue linked glycosidically to the $C_{(6)}$ of a D-galactose residue (I; R = H). A partly methylated derivative of this substance, 6-(2 : 3-dimethyl D-glucuronosido) 2 : 4-dimethyl D-galactose (I; R = Me) was identified amongst the products of hydrolysis of the methylated degraded gum. The same derivative was very probably present in the products of hydrolysis of the methylated gum itself (see below).

Methanolysis of the methylated gum, followed by fractional distillation of the methyl-glycosides, led to the identification of the following sugar derivatives amongst the products of hydrolysis: (*a*) 2 : 3 : 5-trimethyl L-arabinose (II), identified after oxidation as crystalline 2 : 3 : 5-trimethyl L-arabonolactone and as the crystalline amide thereof, (*b*) 2 : 3 : 4-trimethyl D-xylose (III), isolated as the crystalline sugar, (*c*) 2 : 5-dimethyl L-arabinose (IV), identified after conversion into the crystalline lactone and the derived phenylhydrazide and amide, (*d*) 2 : 4 : 6-trimethyl D-galactose (V), isolated as the crystalline anilide, (*e*) 2 : 4-dimethyl D-galactose (VI) (crystalline), the identity of which was confirmed by its conversion into the corresponding crystalline anilide, (*f*) 2 : 3-dimethyl D-glucuronic acid (VII), identified as the crystalline methyl ester from 2 : 3-dimethyl D-saccharolactone, and (*g*) 2-methyl L-arabinose (VIII). The glycoside of this material was found admixed with the glycoside of 2 : 4-dimethyl D-galactose, the physical properties of which are very similar. It was separated from the latter material by converting it into the 3 : 4-*iso*propylidene compound by treatment with acetone in the presence of hydrochloric acid. 2 : 4-Dimethyl methyl-D-galactoside does not form an *iso*propylidene derivative under these conditions (since it does not possess the requisite grouping of *cis*-hydroxyl groups

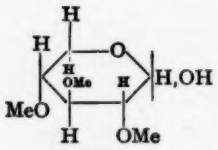
on adjacent carbon atoms), and the low boiling point of the *iso*propylidene derivative facilitates separation from the methylated methylgalactoside. The identity of the 2-methyl L-arabinose



(I.)



(II.)



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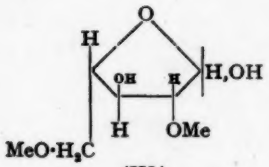
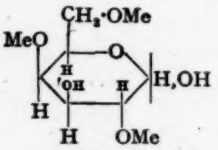


(IV.)



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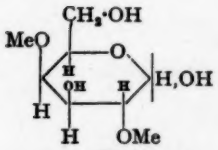
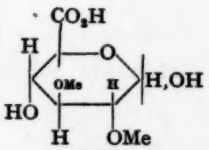
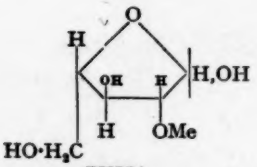


(VI.)



(VII.)



(VIII.)

was confirmed by its conversion into the crystalline toluene-*p*-sulphonylhydrazone (Jones, Kent, and Stacey, *J.*, 1947, 1341).

Quantitative analysis of the mixture of substances (*a*)—(*g*) is a formidable task and is not yet complete, but it is possible to estimate in some cases the molecular proportions. For example, the arabinose derivatives, namely 2 : 3 : 5-trimethyl, 2 : 5-dimethyl, and 2-methyl arabinose, appear to be present in the ratios of approximately 1 : 1 : 1. The proportion of 2 : 3 : 4-trimethyl D-xylose present is, as yet, uncertain, but some indication can be obtained in the following way. In Part I it was shown that potassium periodate attacked the gum with the formation of one mole of formic acid per equivalent of 1200. This formic acid must come from a system in which hydroxyl groups are present on each of three contiguous carbon atoms. Such a grouping is present in an end-group of D-xylopyranose and it is probable, therefore, that all the D-xylose residues are present as end-groups and that the ratio of 2 : 3 : 4-trimethyl D-xylose to 2 : 3 : 5-trimethyl L-arabinose is 1 : 1. Furthermore, in Part I, it was shown that the gum, on oxidation, consumed 5 moles of periodate. The xylopyranose end-group will consume 2 moles of periodate, the arabofuranose end-group will consume one mole, since it contains only one α-glycol grouping, and the uronic acid residue, which contains a similar grouping, will also consume one mole. This accounts for four of the five moles of periodate consumed. The remaining grouping oxidised by the periodate has yet to be identified. The oxidised gum gave no D-xylose on hydrolysis, but it did give some L-arabinose and some D-galactose, though the yields of these sugars were not as high as would have been expected from the weights of 2 : 5-dimethyl and 2-methyl L-arabinose and from the weight of D-galactose derivatives isolated in the present work. The low yields may have been due to the destruction of the sugars under the drastic conditions necessarily employed to hydrolyse the oxidised gum. Estimation of the number of primary hydroxyl groups in the polysaccharide by the method of Lindstedt (*Arkiv Kemi, Min., Geol.*, 1945, **20**, *A*, No. 13) had indicated that four were present per equivalent of 1200. Three of these are supplied by the arabinose end-group (one), the arabinose substituted through $C_{(1)}$ and $C_{(3)}$ (one), and the galactose residue substituted through $C_{(1)}$ and $C_{(3)}$ (one). The position occupied by the fourth triphenylmethyl group is unknown.

Hydrolysis of the methylated degraded gum (arabinose-free) gave 2 : 3 : 4 : 6-tetramethyl D-galactose and 2 : 3 : 4-trimethyl D-galactose. These two sugars do not occur amongst the products of hydrolysis of the methylated gum itself, and it follows that the arabinose and xylose residues in the undegraded gum must be joined through $C_{(6)}$ and $C_{(3)}$ of the D-galactose residues

present in the degraded gum. The isolation of 2 : 3-dimethyl D-glucuronic acid from both the methylated degraded and undegraded gum shows that side-chains of L-arabinose or D-xylose residues are not attached to the acidic residue in the gum. Hydrolysis of the methylated gum left a relatively stable acidic nucleus which on further hydrolysis gave 2 : 4-dimethyl D-galactose and 2 : 3-dimethyl D-glucuronic acid. This is strong indication that an aldobionic acid built up of these two residues is liberated on hydrolysis of the methylated gum. An aldobionic acid containing these two residues is also produced on hydrolysis of the methylated degraded gum indicating that the D-glucuronic acid residue and the D-galactose residue are attached to D-galactose residues and not to pentose residues, since the latter are absent in the degraded material.

Methylated egg plum gum, therefore, resembles methylated cherry gum in that it yields 2 : 5-dimethyl L-arabinose on hydrolysis, as well as L-arabofuranose and D-xylopyranose end-groups. It resembles gum arabic in that the D-glucuronic acid residue is combined through $C_{(6)}$ of a D-galactose residue.

The residues which occur in its molecular structure are A1, $5A^1_3$, 3A1, X1, 3G1, $6G^1_3$, 4GL1, where A = an arabofuranose residue linked as indicated, X = a xylopyranose residue, G = a galactopyranose residue, and GL = a glucuronic acid residue. Some insight has been gained, by the method indicated above, of the mode of occurrence of these residues in the gum, but pending the acquisition of exact quantitative data no unique structural formula can be advanced.

Experimental.

Methylation of Egg Plum Gum.—(All boiling points recorded are bath temperatures.) The gum (36·5 g., from one tree) was dissolved in water (200 c.c.) containing N-thallous hydroxide (30 c.c.), and to the solution was added hot 4N-thallous hydroxide (200 c.c.). The precipitated thallium derivative was filtered off, washed with alcohol, and dried under reduced pressure in the absence of light. The dried material was powdered (120 mesh) and the product boiled under reflux with methyl iodide until the thallium derivative no longer reacted alkaline to litmus. Excess of methyl iodide was distilled off, the residue was extracted first with acetone and then with methyl alcohol, and the extracts were concentrated, yielding a solid (30 g.). This product was further methylated by dissolving it in ethyl alcohol containing N-thallous ethoxide (400 c.c.), and the solution evaporated to a solid which was boiled with methyl iodide until the thallium no longer showed an alkaline reaction. Methyl iodide was removed by distillation, and the methylated gum (yield, 30 g.; Found : OMe, 36·6%) isolated from the residue by extraction with acetone. Repetition of the last methylation procedure, followed by methylation of the product with silver oxide and methyl iodide, gave a pale cream-coloured powder (29·4 g.; Found : OMe, 40·4%. A fully methylated gum containing 4 pentose residues, 3 hexose residues, and one uronic acid residue, and with equivalent weight 1470 requires OMe, 42·4%). This *product* was essentially homogeneous since the fractions obtained from chloroform solution by the addition of light petroleum (b. p. 40—60°) possessed the same properties. $[\alpha]_D^{20°}$ −33° (*c*, 1·1 in methyl alcohol).

Hydrolysis of the Methylated Polysaccharide.—A portion of the methylated polysaccharide (8·2 g.) was dissolved in methanolic hydrogen chloride (1%; 250 c.c.), and the solution boiled under reflux. $[\alpha]_D$ was −33° (initial value), −13° (2 hours), −2° (4 hours), +3° (5½ hours), +5° (6½ hours), and +6° (8 hours). The cooled solution was neutralised with an ice-cold ethereal solution of diazomethane, and the solution evaporated to a syrup on the boiling water-bath at atmospheric pressure to avoid loss of fully methylated pentoses. The residual syrup was dissolved in aqueous barium hydroxide and heated at 60° for 3 hours to convert esters of the uronic acids into the corresponding barium salts. The cooled solution was neutralised with carbon dioxide, filtered from barium carbonate, and the filtrate extracted exhaustively with light petroleum (b. p. 40—60°) in an automatic apparatus. Concentration of the extract gave a syrup (*A*; 1·76 g.), $n_D^{17°}$ 1·4361. Further extraction of the aqueous solution with ether yielded first a fraction (*B*) (1·28 g.), $n_D^{21°}$ 1·4505, and then a fraction (*C*) (0·41 g.), $n_D^{17°}$ 1·4570, on further extraction with the same solvent. The aqueous solution was then concentrated under reduced pressure, and the dry residue exhaustively extracted with ether yielding a syrup (*D*) (1·93 g.), $n_D^{20°}$ 1·4709. The residue (3·8 g.) consisted of inorganic material, together with barium salts of oligosaccharides which had escaped hydrolysis with methyl-alcoholic hydrogen chloride. The mixture was extracted with boiling methyl alcohol, yielding a soluble fraction (*X*; 3·10 g.; Found : Ba, 12·8%) and an insoluble inorganic residue (*Y*; 0·70 g.).

Examination of Fractions A, B, C, *and* D.—Fraction *A* (1·76 g.) was distilled from a Widmer flask yielding fraction I (1·63 g., b. p. 150°/13 mm., $n_D^{18°}$ 1·4338, $[\alpha]_D^{20°}$ −55° (in water) (Found : OMe, 60·8%); syrup *B* was then added to the still residue and the distillation continued yielding fraction II (0·25 g., b. p. 170°/14 mm., $n_D^{17°}$ 1·4468 (Found : OMe, 52·3%), fraction III (0·81 g., b. p. 125°/0·3 mm., $n_D^{17°}$ 1·4500 (Found : OMe, 49·7%), fraction IV (0·29 g., b. p. 130°/0·3 mm., $n_D^{28°}$ 1·4470 (Found : OMe, 48·0%), fraction V (0·44 g., b. p. 160°/0·3 mm., $n_D^{28°}$ 1·4516 (Found : OMe, 47·0%). Fraction *D* was added to the still-residue, and distillation continued, yielding fraction VI (1·90 g., b. p. 190°/0·1 mm., $n_D^{21°}$ 1·4707, $[\alpha]_D$ +108° (in water) (Found : OMe, 39·4%).

Fraction I. Fraction I was combined with the fractions of high methoxyl content and low refractive index isolated from fractions II, III, and IV (see below). A portion (1·01 g.) of these combined fractions was dissolved in hydrobromic acid (0·04 N.), and the solution boiled under reflux. $[\alpha]_D$ was −55° (initial value), −43° (1½ hours), −26° (5 hours), −24° (7 hours), and −24° (7½ hours). These conditions caused hydrolysis of all the trimethyl methyl-L-arabofuranoside and of some of the trimethyl methyl-D-xyloside. The cooled solution was neutralised with silver carbonate and filtered, and the filtrate concentrated to

a syrup (0·70 g.). The cooled solution was oxidised with alkaline iodine by the method of Moore and Link (*J. Biol. Chem.*, 1940, **133**, 293). Excess of iodine was removed by the passage of sulphur dioxide, and the solution neutralised with potassium hydroxide. The solution was then concentrated to dryness, and the solid residue (*S*) extracted with light petroleum (b. p. 40—60°), yielding a syrup (0·10 g.), $n_D^{13°}$ 1·4390. Hydrolysis of this syrup with boiling N-sulphuric acid gave 2 : 3 : 4-trimethyl D-xylose, m. p. and mixed m. p. 91°, after recrystallisation from ether.

The solid residue (*S*) was dissolved in water, acidified with dilute sulphuric acid and extracted with chloroform. Concentration of the extracts left a syrup (0·40 g.), which crystallised on distillation and then had m. p. 31°, not depressed on admixture with 2 : 3 : 5-trimethyl L-arabonolactone. Fraction I, therefore, consisted of a mixture of 2 : 3 : 5-trimethyl L-arabinose and 2 : 3 : 4-trimethyl D-xylose.

A portion (0·35 g.) was hydrolysed with boiling N-sulphuric acid, $[\alpha]_D$ −55° → −25° (constant value; 2 hours). The cooled solution was neutralised with barium carbonate and filtered, and the filtrate concentrated under reduced pressure to a syrup, $[\alpha]_D$ −30° (in water) (Found: OMe, 47·2%). The optical rotation indicated that fraction I contained *ca.* 15% of 2 : 3 : 4-trimethyl D-xylose.

Fraction II. The methoxyl value (52·3%) and the refractive index ($n_D^{17°}$ 1·4468) indicated that this fraction was a mixture of trimethyl and dimethyl methylpentoside. The syrup was dissolved in water, and the solution extracted with light petroleum (b. p. 40—60°). The extract (0·08 g.) was added to fraction I (see above), and the residual aqueous solution was evaporated to a syrup (0·17 g.) which was added to fractions III and IV.

Fractions III *and* IV. Fraction III, which from its physical constants contained some trimethyl methylpentoside, was dissolved in water, and the solution extracted continuously with light petroleum (b. p. 40—60°). The extracts were concentrated and the syrup (0·10 g.) added to fraction I. The aqueous solution, after extraction, was concentrated, and the residue (0·71 g.) was combined with fraction IV (0·29 g.). Hydrolysis of the combined fractions (1·00 g.) was carried out with boiling N-sulphuric acid. $[\alpha]_D$ were −15° (initial value), 32° (1 hour), and 35° (2 hours), the solution then became too dark for further polarimetric readings. After 2½ hours the cooled solution was neutralised with barium carbonate and filtered, and the filtrate concentrated to a syrup, $[\alpha]_D^{20°}$ +43° (in water), $n_D^{23°}$ 1·4690, which did not yield a crystalline anilide on being boiled with alcoholic aniline. A portion (0·30 g.) of the syrup was oxidised with bromine water until the solution was non-reducing. Excess of bromine was removed by aëration, and the solution neutralised with silver carbonate and filtered. After a further filtration, following the passage of hydrogen sulphide, the solution was concentrated under reduced pressure to a syrup which was distilled, b. p. 120°/0·05 mm., $n_D^{18°}$ 1·4480, $[\alpha]_D$ +32° (in water, after ¼ hour), +7·6° (1 hour), ±0° (18¾ hours), −19° (115 hours; constant value) (Found: OMe, 33·0%). Treatment of the lactone with liquid ammonia gave, in small yield, 2 : 5-dimethyl L-arabonamide, m. p. 131°, not depressed on admixture with an authentic specimen. The lactone with alcoholic phenylhydrazine gave 2 : 5-dimethyl L-arabonophenylhydrazide, m. p. and mixed m. p. 162°. This fraction, therefore, contained 2 : 5-dimethyl L-arabinose. Some other sugar, substituted on $C_{(4)}$ by a methoxyl group, must also have been present since the mixture of lactones behaved as if a pyrano-lactone was present. This sugar may have been 2 : 4 : 6-trimethyl D-galactose (see fraction V).

Fraction V. A portion (0·40 g.) of this fraction was hydrolysed with N-sulphuric acid. The change in optical rotation could not be followed owing to the opaqueness of the solution. The reducing sugar was isolated as described above and had $n_D^{27°}$ 1·4717, $[\alpha]_D^{20°}$ 85° (in ethyl alcohol) (Found: OMe, 41·0. Calc. for a trimethyl hexose, OMe, 41·8%). A portion (0·29 g.) of this syrup was boiled for 3 hours with aniline (0·12 g.) in alcohol. Removal of the alcohol left a syrup which rapidly crystallised; m. p. after recrystallisation from a mixture of ether and ethyl alcohol, 175°, alone, or 177—178° admixed with 2 : 4 : 6-trimethyl D-galactose anilide of m. p. 179°. The mixed m. p. with 2 : 3 : 4-trimethyl D-galactose anilide was 135°. This fraction, therefore, consisted mainly, if not entirely, of 2 : 4 : 6-trimethyl D-galactose.

Fraction VI. A portion (0·46 g.) was hydrolysed with boiling N-sulphuric acid (25 c.c.) for 2¾ hours; $[\alpha]_D^{20°}$ +108° → +86°. The reducing sugar was isolated in the usual manner (see above). When this sugar was heated with alcoholic aniline, 2 : 4-dimethyl D-galactose anilide, m. p. 197° (after recrystallisation from water), separated. The optical rotation of the free sugar indicated that an L-arabinose derivative might be present in this fraction. Accordingly a further portion (0·78 g.) of fraction VI was dissolved in acetone (100 c.c.) containing hydrogen chloride (0·45 g.). The reaction, followed polarimetrically, was complete in 1 hour. $[\alpha]_D$ were +108° (initial value), +67° (1 hour; constant value). The solution was poured into aqueous sodium hydrogen carbonate, and, after removal of the acetone on a boiling water-bath, the solution was exhaustively extracted with ether, yielding the fractions (*a*) 0·22 g., $n_D^{17°}$ 1·4588, and (*b*) 0·06 g., $n_D^{18°}$ 1·4628. The aqueous portion was evaporated to dryness and the residue extracted with acetone, yielding fraction (*c*) (0·50 g.).

Fractions (*a*) and (*b*) were combined and hydrolysed with N-sulphuric acid; $[\alpha]_D$ +46° → +71° (2 hours, constant value). The reducing syrup (0·14 g.), isolated as described above, did not crystallise. It was heated at 80° with an aqueous solution of toluene-*p*-sulphonylhydrazide (0·15 g.) in alcohol (10 c.c.) containing acetic acid (1 drop). Removal of the solvent left a syrup which rapidly crystallised. Recrystallisation from aqueous alcohol gave 2-methyl L-arabinose toluene-*p*-sulphonylhydrazone, m. p. 145—147°, not depressed on admixture with an authentic sample (Jones, Kent, and Stacey, *J.*, 1947, 1341).

The syrup (*c*) (0·50 g.) was hydrolysed with N-sulphuric acid, and the reducing sugar isolated as before. When kept, the product crystallised and was identified as 2 : 4-dimethyl D-galactose monohydrate, m. p. 104°, not depressed on admixture with an authentic specimen.

Fraction V, therefore, consists in the main of a mixture of 2 : 4-dimethyl D-galactose and 2-methyl L-arabinose in approximately equal amounts.

Examination of Barium Salt (X).—The barium content (12·8%) of this fraction indicated that some oligosaccharide was present. A portion (1·81 g.) of it was, therefore, dissolved in methanolic hydrogen chloride (5%) and the solution boiled under reflux; $[\alpha]_D$ were +15° (initial value), +23° (1 hour), +37° (3¼ hours), +37° (4¼ hours), +41° (5¼ hours), and +38° (7¼ hours; decomposition). After the

mixture had been cooled, barium chloride was removed by filtration, and the solution was neutralised with silver carbonate. The filtered solution was evaporated to a syrup which was warmed (60°) with 0·3N-barium hydroxide (50 c.c.) for 3 hours, to convert esters of the uronic acids into the corresponding barium salts. After the mixture had cooled, the excess of barium hydroxide was removed by carbon dioxide, and the precipitated barium carbonate filtered off. The filtrate was then evaporated to dryness under reduced pressure, and the residue (1·81 g.) was extracted exhaustively with dry ether, yielding fraction (*P*) (0·64 g.), $n_D^{23°}$ 1·4775, and a residue (*Q*) (1·17 g.; Found: Ba, 18·9; OMe, 26·6%). These analytical figures indicate that the barium salt (*Q*) still contained some oligosaccharide.

The methylglycosides (*P*, 0·64 g.) were hydrolysed by boiling N-sulphuric acid; $[\alpha]_D$ +77° → +78° (constant value, 1½ hours). The reducing sugars, isolated in the usual manner, gave, on boiling with alcoholic aniline, 2 : 4-dimethyl D-galactose anilide, m. p. 198°, not depressed on admixture with an authentic specimen. The refractive index of (*P*) indicated that some other sugar of lower methoxyl content was probably also present.

The barium salt (*Q*; 1·17 g.) was converted into the corresponding methyl ester by boiling methanolic hydrogen chloride (1%) (4 hours). The solution was neutralised with silver carbonate, and the filtered solution concentrated under diminished pressure to a syrup which was dissolved in acetone. The purified syrup gave, on distillation, a fraction (0·76 g.), b. p. 140—150°/0·05 mm., $n_D^{15°}$ 1·4582 (Found: OMe, 47·4. Calc. for the methyl ester of dimethyl methylglucuronoside: OMe, 49·6%). The still-residue (0·20 g.) consisted of oligosaccharide which had escaped hydrolysis.

The ester (0·76 g.) was hydrolysed with N-hydrochloric acid; $[\alpha]_D$ +57° → + 41° (constant value after 3 hours). The cooled solution was neutralised with silver carbonate and filtered. Silver was removed by hydrogen sulphide, and the silver sulphide by filtration. Concentration of the filtrate gave syrupy 2 : 3-dimethyl D-glucuronic acid, identified by the following procedure. A portion (0·30 g.) of the hydrolysed syrup was oxidised with bromine water until the solution was non-reducing. Excess of bromine was removed by aëration, and the solution was neutralised with silver carbonate and filtered. The filtrate was treated with hydrogen sulphide to remove silver and was then concentrated under diminished pressure to a syrup, which was esterified by boiling methanolic hydrogen chloride (1%). The cooled solution was neutralised with silver carbonate and filtered. The ester, obtained on concentration of the filtrate, was distilled in a high vacuum, yielding a syrup, $n_D^{15°}$ 1·4598, which slowly crystallised and then had $[\alpha]_D^{20°}$ +14° (in water) and m. p. 101°, alone or admixed with 2 : 3-dimethyl saccharolactone methyl ester. The uronic acid fraction, therefore, contains 2 : 3-dimethyl D-glucuronic acid, and some of this acid is combined with 2 : 4-dimethyl D-galactose. It is not possible from the evidence available to decide whether or not other derivatives of D-glucuronic acid are also present.

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377. *Cholla Gum.*

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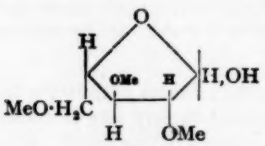
Cholla gum, an exudate of the cactus, *Opuntia fulgida*, has been shown to consist of L-arabinose (6 parts), D-xylose (2 parts), L-rhamnose (trace), D-galactose (3 parts), and D-galacturonic acid (1 part) in the approximate proportions indicated. Hydrolysis of the methylated derivative of cholla gum yields 2 : 3 : 5-trimethyl L-arabinose (4 parts), 2 : 3 : 4-trimethyl D-xylose (2 parts), 2 : 3-dimethyl L-arabinose (1 part), 2 : 4-dimethyl D-galactose (3 parts), L-arabinose (1 part) and 2-methyl D-galacturonic acid (1 part). The L-arabinose residues are present in the furanose form, and the remainder of the sugars are in the pyranose form. Cholla gum, therefore, resembles other plant gums in many features of its architecture, the main difference being that its acidity is due to D-galacturonic acid instead of D-glucuronic acid.

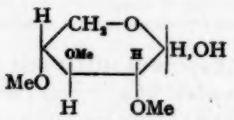
THE work of Smith (*J.*, 1939, 744, 1724; 1940, 1035) and Jackson and Smith (*J.*, 1940, 74, 79) on the structure of gum arabic, an exudate of a tropical member of the family Leguminosæ has shown that the polysaccharide resembles closely the gums exuded by trees of the family Rosaceæ growing in temperate climates (Hirst, *J.*, 1942, 70). Cholla gum is of tropical origin and is exuded on the white cactus, *Opuntia fulgida*, a native of Mexico and of the Southern States of America, and it was of interest, therefore, to see whether a similar type of structure is present. The formation of the gum seems to be favoured by prolonged hot dry spells and, although its function in the economy of the cactus is unknown, it may be that in periods of drought it enables the plant to resist desiccation. Through the kindness of Dr. K. Folkers, and of Dr. B. A. Krukoff of the New York Botanical Garden, we were able to obtain samples of this material. Cholla gum has been examined previously by Anderson and Sands (*Amer. J. Pharm.*, 1925, **97**, 589) and by Klaas and Sands (*J. Amer. Chem. Soc.*, 1929, **51**, 3441), but as the properties of their material differed in some respects (particularly in optical rotation) from our sample we decided to examine our polysaccharide in some detail. The gum was purified by precipitation from acid

solution by the addition of alcohol, yielding an acidic polysaccharide as a white powder which was easily soluble in water and showed a negative rotation ($[\alpha]_D$ −80°). Similar analyses were obtained on examination of samples prepared from different nodules of the crude gum. One component only was detected on electrophoretic examination, carried out by Dr. F. A. Isherwood, to whom we are indebted for these results. On hydrolysis with dilute acid the gum gave a mixture of sugars amongst which L-arabinose, D-xylose, D-galactose, and D-galacturonic acid were detected. A trace of L-rhamnose was also present. It may be noted that Klaas and Sands (*loc. cit.*) did not detect D-xylose but found instead L-rhamnose (5·5%) in the products of hydrolysis of the sample they examined. The separation, identification, and estimation of the component sugars of the polysaccharide was greatly facilitated by the use of the paper chromatographic technique (Partridge, *Nature*, 1946, **158**, 270; *Biochem. J.*, 1948, **42**, 238; Flood, Hirst, and Jones, *Nature*, 1947, **160**, 86; *J.*, 1948, 1679). By this method it was shown that our sample of cholla gum contained the following sugars in the proportions indicated: L-arabinose (6 parts), D-xylose (2 parts), D-galactose (3 parts), D-galacturonic acid (1 part), and L-rhamnose (trace). Traces of other sugars may also be present. On boiling the gum acid with dilute acids, L-arabinose, D-xylose, and D-galactose were first liberated leaving a more resistant nucleus of D-galactose and D-galacturonic acid which was split on further hydrolysis with stronger acid into its component parts. It follows that Cholla gum resembles closely other plant gums (cf. Hirst and Jones, *J. Soc. Dyers and Col.*, 1947, **63**, 249) in that it contains D-xylose and L-arabinose, both of which are liberated from the polysaccharide on acidic hydrolysis with relative ease. It differs, however, from other gums examined by us in the structure of the nucleus, which is more resistant to acidic hydrolysis and consists of residues of D-galactose and D-galacturonic acid. D-Glucuronic acid is absent, cholla gum displaying in this respect a similarity to the plant mucilages rather than to the gums hitherto examined (compare, however, gum tragacanth, which also contains D-galacturonic acid; James and Smith, *J.*, 1945, 739).

Information concerning the mode of linkage of the various component sugars in the molecule was obtained from an examination of the products of hydrolysis of the fully methylated polysaccharide. As was expected, hydrolysis of the methylated derivative gave a complex mixture of sugar derivatives, which could be separated in the pure state only with great difficulty. Quantitative estimates of the proportions in which the various sugar residues are present can, therefore, be only approximate at this stage. Nevertheless, from a study of the physical constants of the various sugars identified and from an examination of the different fractions obtained by extraction and distillation of the mixture produced on methanolysis of the polysaccharide a rough estimate can be made. By these methods of fractionation, followed by hydrolysis of the methylglycosides, the following sugars were identified in the approximate molecular proportions given in parentheses: (1) 2 : 3 : 5-trimethyl L-arabinose (I) (4 parts), identified, after oxidation with bromine water, as the crystalline lactone of 2 : 3 : 5-trimethyl L-arabonic acid; (2) 2 : 3 : 4-trimethyl D-xylose (II) (2 parts), isolated as the crystalline sugar, whose identity was confirmed by oxidation to the crystalline lactone of 2 : 3 : 4-trimethyl D-xylonic acid; (3) 2 : 3-dimethyl L-arabinose (1 part) [shown in (III) as the furanose form to indicate the mode of linkage in the polysaccharide], identified after oxidation to 2 : 3-dimethyl L-arabonic acid and conversion into the amide; (4) 2 : 4-dimethyl D-galactose (IV) (3 parts), whose identity was



(I.)



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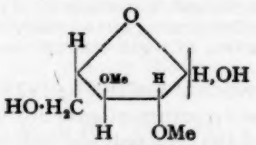

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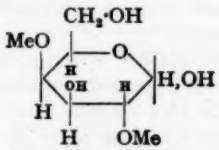
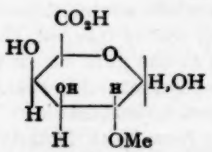


(IV.)



(V.)

confirmed by isolation of the crystalline sugar, by conversion into the crystalline anilide, and by oxidation of the sugar to 2 : 4-dimethyl D-galactonic acid, identified as its crystalline amide;

(5) L-arabinose (1 part) (unsubstituted), isolated as its benzoylhydrazone; and (6) 2-methyl D-galacturonic acid (V) (1 part), identified as the diamide of 2-methyl D-galactosaccharic acid. 2 : 4-Dimethyl D-galactose was also found combined with 2-methyl D-galacturonic acid in the form of an aldobionic acid [compare the aldobionic acid derivative produced on hydrolysis of degraded egg plum gum (Hirst and Jones, *J.*, 1948, 120)].

The D-xylose residues are present in the pyranose form as end-groups, and the major portion (probably all) of the L-arabinose residues are of the furanose type and most of them are present as end-groups. A proportion of the arabinose is combined in the furanose form through $C_{(1)}$, $C_{(3)}$, $C_{(3)}$, and $C_{(5)}$ (V). This type of combination in which every hydroxyl group, other than that concerned with ring formation, is combined with another sugar residue has hitherto been encountered only rarely, but it is found in the polysaccharide present in ovomucoid (Stacey and Wooley, *J.*, 1942, 550) and in slippery-elm mucilage (Brown, Hirst, Hough, Jones, and Wadman, *Nature*, 1948, **161**, 720).

In the present instance the absence of monomethyl arabinose is further evidence that fully substituted arabinose residues are actually components of the gum molecule and that the isolation of the free arabinose after hydrolysis is not to be attributed to incomplete methylation.

Cholla gum resembles damson gum (Hirst and Jones, *J.*, 1946, 506) in that it contains L-arabofuranose residues linked through $C_{(5)}$ and $C_{(1)}$ (III). The D-galactose residues are triply linked through $C_{(1)}$, $C_{(3)}$, and $C_{(6)}$ (IV), $C_{(2)}$ and $C_{(4)}$ of the D-galactose being unsubstituted in the gum molecule. It appears, therefore, that D-galactose favours the 1 : 3- and 1 : 6-type of linkage typical of its occurrences in other gums. The uronic acid residue (V) is linked through three positions $C_{(1)}$, $C_{(3)}$, and $C_{(4)}$. On only one other occasion hitherto has this acid been detected amongst the products of hydrolysis of methylated gum, namely by James and Smith (*loc. cit.*) in the hydrolysis products of methylated tragacanthic acid. Cholla gum, therefore, differs in this respect from the other gums which have been investigated, since these have contained D-glucuronic acid residues linked only through either $C_{(1)}$ or $C_{(1)}$ and $C_{(4)}$. Cholla gum, therefore, shows certain divergences from the gums exuded on trees of the family Rosaceæ in temperate climates.

At this stage it is not possible to formulate a unique structure for the polysaccharide, but the isolation of large amounts of end-group (I and II) shows that the molecule must be of the highly branched type.

Experimental.

Purification of the Gum.—The crude gum was dark brown, and has a characteristic odour. It was purified by dissolving the powdered material in warm dilute aqueous sodium hydroxide, during which process ammonia was evolved and silica was precipitated. It is not known whether this silica was combined with the gum or whether it was dust which had been trapped in the sticky gum when it was first exuded. The solution of gum was then filtered, and the cooled filtrate acidified with cold dilute hydrochloric acid, whereupon the colour changed from dark brown to clear light yellow. The polysaccharide was precipitated by the addition of methyl alcohol (3 volumes) to the vigorously stirred solution. The product was washed twice by decantation, filtered off, dissolved in cold water, and reprecipitated by the addition of methyl alcohol with stirring. The pale cream-coloured product was filtered off, washed with acetone and ether, and dried at 40° in a vacuum-oven. Four separate nodules in addition to a large batch of gum were purified in this manner. No significant differences in properties were observed. The pure gum had $[\alpha]_D^{15°}$ −82° in water (as sodium salt), $[\alpha]_D^{15°}$ −83° in water as free acid; furfuraldehyde liberated by boiling 12% hydrochloric acid, 40%; uronic anhydride, 10·4%; OMe, <1%; N, <0·2%; ash (weighed as sulphate), 2·5%.

Examination of a sample of the gum in the Tiselius electrophoretic apparatus indicated that the polysaccharide was homogeneous (experiments carried out by Dr. F. A. Isherwood).

Hydrolysis of the Gum.—The purified gum (3·65 g.) was dissolved in 0·01N-sulphuric acid (100 c.c.), and the solution was boiled under reflux. The viscosity of the solution fell rapidly. $[\alpha]_D^{11°}$ were −82° (initial value), −66° (1 hour), −23° (2½ hours), +4° (4½ hours), +25° (6½ hours), +37° (7½ hours), +49° (8½ hours), +51° (9½ hours), +53° (10 hours). Hydrolysis was much slower after this stage. The solution was neutralised with barium carbonate and filtered. The filtrate was concentrated at 40°, under reduced pressure, to a syrup (4·01 g.) which was exhaustively extracted with boiling methyl alcohol, to give a soluble fraction *A* (2·71 g.), $[\alpha]_D$ +45° in water, and an insoluble fraction *B* (1·30 g.) (Found for *B*: Ba 12·3%; a trisaccharide containing two hexose units and one hexuronic acid residue requires Ba, 11·7%).

Examination of fraction A. Fraction *A* (2·71 g.) was boiled with N-sulphuric (50 c.c.), the hydrolysis being followed polarimetrically: $[\alpha]_D$ +45° (initial value); +63° (30 minutes); +67° (90 minutes) (constant value). This change in optical rotation indicates that fraction (*A*) contained some oligosaccharide. The solution was neutralised with barium carbonate and filtered, and the filtrate was evaporated to a syrup (2·71 g.; $[\alpha]_D$ +72° in water) under reduced pressure. A portion of this material was examined on the paper chromatogram which revealed the presence of arabinose, xylose, and galactose. The presence of these sugars was confirmed in the following ways: (*a*) by the isolation of crystalline L-arabinose, m. p. 154°, $[\alpha]_D^{27°}$ +103° (equilibrium value in water), and by the formation of L-arabinose benzoylhydrazone, m. p. 186° (decomp.) (0·23 g.), from a portion of the syrup (0·24 g.) (the fraction contained, therefore, 65% of L-arabinose); (*b*) D-galactose was detected and estimated as its phenylmethylhydrazone, m. p.

187° (0·53 g. syrup gave 0·63 g. of derivative corresponding to the presence of 0·049 g. of D-galactose after correcting for the presence of L-arabinose phenylmethylhydrazone; cf. Hirst, Jones, and Woods, *J.*, 1947, 1048); and (*c*) D-xylose was detected by the formation of its sparingly soluble dibenzylidene dimethyl acetal, m. p. 211°, $[\alpha]_D^{20°}$ −9° (in chloroform) (Breddy and Jones, *J.*, 1945, 738; Wise and Ratcliff, *Ind. Eng. Chem., Anal. Ed.*, 1947, **19**, 694). An independent estimation of the sugars was carried out by the paper chromatogram method (Flood, Hirst, and Jones, *loc. cit.*). The sugars were found to be present in the relative proportions, L-arabinose (6 parts), D-xylose (2 parts), and D-galactose (1 part).

Examination of insoluble fraction B. A portion (0·52 g.) of this fraction was dissolved in 0·1N-sulphuric acid, and the precipitated barium sulphate filtered off. The filtrate was boiled under reflux, and the reaction was followed polarimetrically: $[\alpha]_D$ +38° (initial value); +49° (2 hours); +61° (5 hours); +74° (9 hours); +76° (10½ hours). The cooled solution was neutralised with barium carbonate and filtered, and the filtrate concentrated under reduced pressure. The resulting syrup (0·53 g.) was extracted with boiling methyl alcohol, and the extracts were concentrated under reduced pressure to a syrup (0·17 g.), $[\alpha]_D$ +75° (in water), which, by examination on the paper chromatogram, was found to contain mainly D-galactose, with traces of arabinose, xylose, and rhamnose. The undissolved barium salt [0·26 g.; $[\alpha]_D$ +73° (in water) (Found: Ba, 17·3%; the barium salt of an aldobionic acid requires Ba, 16·2%)] was hydrolysed by boiling 2N-sulphuric acid (6·3 c.c.), the hydrolysis being followed polarimetrically: $[\alpha]_D$ +74° (initial value); +68° (30 minutes); +53° (1 hour); +52° (1½ hours, constant value). The cooled solution was neutralised with barium carbonate and filtered, and the filtrate evaporated giving a solid (0·11 g. from 0·18 g. of barium salt) which was extracted with methyl alcohol. The extracted material (0·044 g.) was a syrup which contained galactose and a trace of rhamnose, both identified on the paper chromatogram. The residual barium salt (0·068 g.), $[\alpha]_D$ +74° (in water) (Found: Ba, 27·1; the barium salt of a hexuronic acid requires Ba, 26·2%), was converted into the acid by adding the calculated quantity of 0·01N-sulphuric acid and the filtered solution was treated with bromine water. After several days the precipitate of mucic acid was filtered off, washed, and dried; m. p. 215°, undepressed on admixture with an authentic specimen. The presence of barium D-galacturonate was confirmed by the formation of a brick-red precipitate on warming the barium salt with basic lead acetate solution (Ehrlich, *Ber.*, 1932, **65**, 352).

Methylation of Cholla Gum.—The purified gum (25 g.) was dissolved in water (300 c.c.) and methylated at 20° by the portionwise addition, with vigorous stirring, of 30% aqueous sodium hydroxide (400 c.c.) and methyl sulphate (200 c.c.). After addition of the reagents stirring was continued for 12 hours and the solution was then concentrated on a steam-bath. The concentrate was treated (conditions as above) with methyl sulphate (200 c.c.) and 30% aqueous sodium hydroxide (400 c.c.). After two further methylations a crude gummy product was isolated by heating the solution on the boiling water-bath. Methylation was completed by evaporating to dryness a solution of the material in benzene containing thallous ethoxide (1·7N.; 100 c.c.), and boiling the residual solid (powdered, 80 mesh) with methyl iodide, until the insoluble material no longer gave an alkaline reaction to litmus paper. The methylated derivative was isolated by concentration of the filtered solution (Found: OMe, 38·4%). An attempt was made to fractionate the methylated polysaccharide by heating it with N-sodium hydroxide (50 c.c.) and extracting the resultant solution with chloroform. Concentration of the extract gave a fraction of methylated cholla gum (I) which had properties very similar to those of the fraction II obtained after further extraction of the acidified aqueous solution [fraction I, $[\alpha]_D^{20°}$ − 110° ± 5° (in methyl alcohol) (Found: OMe, 38·4%); fraction II, $[\alpha]_D^{20°}$ − 100° ± 5° (in methyl alcohol) (Found: OMe, 38·1%)]. In view of the similarity in properties and of the failure to detect heterogeneity by electrophoretic experiments on the original gum, these fractions were recombined for further examination.

Hydrolysis of the Methylated Polysaccharide.—The following details are typical of several experiments. Methylated cholla gum (14·17 g.) was dissolved in methanolic hydrogen chloride (1%; 300 c.c.), and the solution was boiled under reflux for 8 hours. It was not possible to follow the reaction polarimetrically owing to the darkness of the solution. The solution was then cooled and hydrogen chloride was removed by the addition of an ice-cold solution of diazomethane in ether. The solvents were removed by evaporation on the boiling water-bath at atmospheric pressure. The last traces of solvent were removed under reduced pressure, and the residual syrup was heated with 0·3N-barium hydroxide (60 c.c.) at 60° for 3 hours to convert the esters of the uronic acid derivatives into the corresponding barium salts. A stream of carbon dioxide was then passed through the solution to remove the excess of barium hydroxide, and the solution was filtered. The filtrate was exhaustively extracted with purified light petroleum (b. p. 40—60°), yielding a fraction (*A*) (7·15 g.), $n_D^{20°}$ 1·4353, soluble in light petroleum. Extraction of the aqueous solution with ether then yielded an ether-soluble fraction (*B*) (1·38 g.), $n_D^{20°}$ 1·4490. The aqueous solution was then evaporated to dryness, and the solid residue was exhaustively extracted with dry ether, yielding a soluble fraction (*C*) (3·89 g.) and an insoluble residue (*D*) (2·9 g.), which was purified by dissolving it in methyl alcohol and filtering off traces of barium carbonate. The product, after removal of the methyl alcohol, had Ba, 17·3, and OMe, 22·3%.

Examination of fractions A *and* B. (All distillation temperatures recorded are bath temperatures.) Fraction *A* (7·15 g.) was distilled from a Widmer flask, yielding fraction I (6·65 g.), b. p. 150°/20 mm., $n_D^{20°}$ 1·4347, $[\alpha]_D^{20°}$ −43° (in water) (Found: OMe, 60·0%). Fraction *B* was then added to the Widmer flask, and the distillation was continued yielding fraction II*a* (0·46 g.), b. p. 150—160°/24 mm., $n_D^{21°}$ 1·4362 (Found: OMe, 57·0%). A portion (1·06 g.) of the still-residue (1·43 g.) was further fractionated by dissolving it in water and extracting the solution with light petroleum (b. p. 40—60°) for several hours (continuous extraction apparatus). Evaporation of the solvent left a fraction II*b* (0·29 g.) (Found: OMe, 59·8%). The aqueous solution on evaporation gave a syrup (0·75 g.) which was purified by distillation giving fraction III, b. p. 120°/0·1 mm., $n_D^{19°}$ 1·4490 (Found: OMe, 45·2%).

Examination of the fractions produced on distillation. (a) *Fraction* I. A portion (0·13 g.) was boiled with N-sulphuric acid (10 c.c.), the reaction being followed polarimetrically: $[\alpha]_D$ −43° (initial value); −19° (½ hour); −20° (1 hour); −21° (2 hours; constant value). The cooled solution was neutralised with barium carbonate and filtered, and the filtrate evaporated to dryness under reduced pressure. The

residue was extracted with acetone, and the sugars which dissolved were then purified by distillation; $n_D^{19°}$ 1·4522, $[\alpha]_D$ −22° (*c*, 0·6 in water) (Found: OMe, 47·8. Calc. for $C_8H_{14}O_5$: OMe, 48·4%). These figures indicated that the fraction was a mixture of 2 : 3 : 5-trimethyl L-arabinose and 2 : 3 : 4-trimethyl D-xylose. Accordingly a second portion (5·30 g.) of fraction I was boiled in 0·4N-hydrobromic acid (50 c.c.) for 8 hours. Trial experiments had shown that under these conditions methylarabofuranoside was completely hydrolysed, whilst methylxylopyranoside was only partly hydrolysed. $[\alpha]_D$ were −43° (initial value), −39° (1 hour), −25° (3 hours), −18° (5½ hours), −17° (7 hours), and −17° (8 hours). The cooled solution was neutralised with N-sodium hydroxide and evaporated to a syrup under reduced pressure, and the sugars were extracted with acetone and distilled in a vacuum, yielding fraction A_1 (0·61 g.), b. p. 160°/12 mm., $n_D^{16°}$ 1·4490, fraction A_2 (2·34 g.), b. p. 130°/0·2 mm., $n_D^{16°}$ 1·4515, and a still-residue (1·81 g.). The refractive index of fraction A_1 suggested that it contained an appreciable proportion of 2 : 3 : 5-trimethyl L-arabinose and 2 : 3 : 4-trimethyl D-xylose, admixed with the fully methylated methylxyloside. This fraction (A_1) was, therefore, dissolved in water and extracted with light petroleum (b. p. 40—60°) for 2 hours. The extracts on concentration gave a syrup (0·27 g.), $n_D^{18°}$ 1·4440, which was hydrolysed with boiling N-sulphuric acid for 3 hours. Removal of the sulphuric acid as barium sulphate, followed by evaporation of the aqueous solution, gave 2 : 3 : 4-trimethyl D-xylose, m. p. 91° (after recrystallisation from ether), not depressed on admixture with an authentic specimen. Oxidation of this material with bromine water gave 2 : 3 : 4-trimethyl D-xylonolactone, m. p. 55°, not depressed on admixture with an authentic specimen.

Fraction A_2 and the still-residue were combined and oxidised with bromine water until the solution was non-reducing. Bromine was removed by aëration, and the solution was neutralised with silver carbonate and filtered. Hydrogen sulphide was passed through the solution, and the precipitated silver sulphide was filtered off. The filtrate on evaporation gave crystalline 2 : 3 : 5-trimethyl L-arabonolactone, m. p. and mixed m. p. 31°. This was converted by methanolic ammonia into the crystalline amide, m. p. and mixed m. p. 138° (Found: N, 6·4; OMe, 45·3. Calc. for $C_8H_{17}O_5N$: N, 6·7; OMe, 44·5%).

From the equilibrium rotation of the product obtained by acidic hydrolysis of fraction I ($[\alpha]_D$ −22°), it was calculated that this fraction contained 2 : 3 : 5-trimethyl L-arabinose and 2 : 3 : 4-trimethyl D-xylose in the approximate ratio of 2 : 1.

Fractions IIa *and* IIb. These fractions were combined, and a portion (0·29 g.) was boiled with N-sulphuric acid (10 c.c.) for 3 hours; $[\alpha]_D^{20°}$ −30° (initial value), −12° (end value). The cooled solution was neutralised with barium carbonate and filtered and the filtrate was concentrated to a syrup, $[\alpha]_D$ −13° (in water). When this was set aside, crystalline 2 : 3 : 4-trimethyl D-xylose separated and was isolated on porous tile. After recrystallisation from ether it had m. p. 91—92°, not depressed on admixture with an authentic specimen. The non-crystalline material was oxidised with bromine water, and the crude lactone was purified by distillation. The distillate crystallised when kept, giving 2 : 3 : 5-trimethyl L-arabonolactone, m. p. 29°, which was converted by liquid ammonia into 2 : 3 : 5-trimethyl L-arabonamide, m. p. 137°, not depressed on admixture with an authentic specimen.

Fraction III. A portion (0·13 g.) of this fraction was hydrolysed with N-sulphuric acid, the reaction being followed polarimetrically: $[\alpha]_D$ −12° (initial value); +75° (1 hour); +76° (1½ hours, constant value). The solution was neutralised with barium carbonate. Concentration after filtration gave a syrupy mixture of reducing sugars, $n_D^{19°}$ 1·4738 (Found: OMe, 33·7. Calc. for $C_7H_{14}O_5$: OMe, 34·8%). When a portion of this syrup (0·10 g.) was boiled with alcoholic aniline (0·05 g. in 5 c.c.) the anilide of 2 : 3-dimethyl L-arabinose was formed, and crystallised on removal of the solvent; m. p. 137° after recrystallisation from ethyl alcohol, not depressed on admixture with an authentic specimen. A further portion of the syrup (0·16 g.) was oxidised with bromine water, and the lactone of the resultant acid was isolated as described above. On treatment with liquid ammonia the lactone gave 2 : 3-dimethyl L-arabonamide, m. p. (after recrystallisation from acetone–ether) 156°, not depressed on admixture with an authentic sample. It was calculated that fraction III contained about 90% of 2 : 3-dimethyl L-arabinose.

Examination of fraction C. This fraction (3·89 g.) was partly crystalline. The crystalline component (0·22 g.) was separated on porous tile and identified as 2 : 4-dimethyl β-methyl-D-galactoside, m. p. and mixed m. p. 162—164°, $[\alpha]_D$ −4° (in water) (Found: OMe, 42·2. Calc. for $C_9H_{18}O_6$: OMe, 41·9%). This was confirmed by hydrolysing a portion (0·13 g.) with boiling N-sulphuric acid (5 c.c.) for 1 hour: $[\alpha]_D$ −4° ⟶ +77°. Removal of the sulphuric acid as barium sulphate, followed by concentration of the aqueous solution, gave crystalline 2 : 4-dimethyl D-galactose monohydrate, m. p. 104°. The non-crystalline material (3·64 g.) was isolated by exhaustive extraction of the tile with chloroform. The methoxyl content (36·3%) of this syrup showed that some material of lower methoxyl content than dimethyl methyl-D-galactoside was present. This was identified as methyl-L-arabinoside in the following way. A portion of the syrup (1·21 g.) was boiled with N-sulphuric acid ($[\alpha]_D^{20°}$ changed from + 76° to +80°, constant value, in 1½ hours). The syrupy product, isolated in the usual manner, had $[\alpha]_D$ +86° (in water) and the methoxyl content (25·8%) again indicated the presence of some other sugar of a lower methoxyl content than dimethyl D-galactose (OMe, 29·8%). A portion of the syrup crystallised when kept for several days, and the crystals were separated on porous tile. Recrystallisation from acetone gave pure 2 : 4-dimethyl D-galactose monohydrate, m. p. and mixed m. p. 104° [Anilide, m. p. 205° (Found: N, 5·2; OMe. 22·1. Calc. for $C_{14}H_{21}O_5N$: N, 5·0; OMe, 21·9%)]. The tile was extracted with methanol, and the extract boiled with methanolic hydrogen chloride (3%). After four hours the solution was cooled, neutralised with silver carbonate, and filtered. On evaporation of the solvent a syrup was obtained from which crystalline β-methyl-L-arabinoside separated, m. p. and mixed m. p., after recrystallisation from aqueous alcohol, 168—170° (Found: OMe, 18·7. Calc. for $C_6H_{12}O_5$: OMe, 18·9%). It is evident, therefore, that the presence of methyl-L-arabinoside in the fraction C is, in part at least, responsible for the low methoxyl content. An estimate of the amount of 2 : 4-dimethyl methyl-D-galactoside present in the syrup removed from the tile may be made from its methoxyl content (36·3%) and from the methoxyl content (25·8%) of the sugars produced on hydrolysis. These figures indicate the presence of *ca.* 85% of the galactose derivative and 15% of the arabinose derivative. This conclusion was confirmed by oxidising a portion (0·313 g.) of the reducing sugars with 0·3M-sodium

periodate (10 c.c.) and determining the formic acid produced [Found: 5·86 mg. (½ hour); 6·38 mg. (1 hour); 7·89 mg. (24 hours)]. A blank experiment on L-arabinose (28 mg.) under similar conditions showed that 74% of the calculated quantity of formic acid is produced in 24 hours. Approximately 14% of L-arabinose was present, therefore, in the mixture of reducing sugars.

Examination of residue D. The analytical figures (Found: Ba, 17·3; OMe, 22·3%) indicated that this fraction was not the pure barium salt of a methylated hexuronic acid (Ba content too low). A portion (1·31 g.) was exhaustively extracted with ether in a Soxhlet apparatus. Evaporation of the ether left a syrup (0·16 g.) identified as 2 : 4-dimethyl methyl-D-galactoside, since on hydrolysis with N-sulphuric acid it gave crystalline 2 : 4-dimethyl D-galactose monohydrate, m. p. and mixed m. p. 104°. The residual barium salt (Found: Ba, 19·0%) was boiled with 4% methanolic hydrogen chloride (25 c.c.) for 8 hours to convert the uronic acid residue into the corresponding methyl ester and to hydrolyse any oligosaccharide. The cooled solution was neutralised with silver carbonate and filtered, and the filtrate evaporated to dryness and dissolved in warm 0·3N-barium hydroxide (30 c.c.) in order to convert any ester into the barium salts. Excess of barium hydroxide was removed with carbon dioxide, and the filtered solution was evaporated to dryness. The residue was extracted exhaustively with ether (continuous extraction apparatus) to remove 2 : 4-dimethyl methyl-D-galactoside (0·22 g.) produced by methanolysis. The residual barium salt (0·91 g.) now analysed as the barium salt of the methylglycoside of a monomethyl galacturonic acid (Found: Ba, 24·6; OMe, 21·3. Calc. for $C_8H_{12}O_7Ba_{\frac{1}{2}}$: Ba, 23·7; OMe, 21·7%). This salt (0·90 g.) was converted into the corresponding ester by boiling methanolic hydrogen chloride (1%; 3 hours). Barium chloride was removed by filtration and the solution was neutralised with silver carbonate and filtered. Evaporation of the solvent now gave a syrup which was distilled in a micro-distillation apparatus (Brown and Jones, *loc. cit.*); b. p. 180°/1 mm., $n_D^{20°}$ 1·4695 (Found: OMe, 38·5. Calc. for $C_9H_{16}O_7$: OMe, 39·4%). The ester on reaction with liquid ammonia gave an amide, m. p. 173°, in small yield. The ester (0·21 g.) was hydrolysed with N-hydrochloric acid (10 c.c.) at 100°: $[\alpha]_D^{20°}$ +21° (initial value); +32° (1¼ hours); +33° (3½ hours, constant value). The cooled solution was neutralised with silver carbonate, and the solution was filtered before and after the passage of hydrogen sulphide. The filtrate was aërated to remove hydrogen sulphide, and the uronic acid was oxidised with bromine water until it no longer reduced Fehling's solution. Silver oxide was then added to remove bromide ions and to convert the acid into its silver salt. The solution was filtered before and after the passage of hydrogen sulphide, and the filtrate concentrated to a syrup which was esterified by boiling it with methyl alcoholic hydrogen chloride. The resultant ester gave, with methyl alcoholic ammonia, the diamide of 2-methyl D-galactosaccharic acid, m. p. and mixed m. p. 195° (Jones and Stacey, *J.*, 1947, 1340).

Summary of Yields.—From optical rotations and methoxyl contents of the various fractions it was calculated that the sample of methylated cholla gum (14·17 g.) had yielded, on methanolysis, approximately the following weights and molecular proportions of sugar derivatives: 2 : 3 : 5-trimethyl methyl-L-arabonoside (5·00 g., 4 mols.); 2 : 3 : 4-trimethyl methyl-D-xyloside (2·50 g., 2 mols.); 2 : 3-dimethyl methyl-L-arabinoside (1·04 g., 1 mol.); 2 : 4-dimethyl methyl-D-galactoside (4·13 g., 3 mols.); methyl-L-arabinoside (0·64 g., 1 mol.); and 2-methyl methyl-D-galacturonoside methyl ester (1·65 g., 1 mol.). These yields and molecular ratios are to be regarded as approximate, in view of the difficulty encountered in separating the various fractions.

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378. *Reactions of Nitroparaffins. Part II. The Reaction of 2-Nitropropane with Formaldehyde and Ammonia.*

By J. K. N. JONES and T. URBAŃSKI.

2-Nitropropane with formaldehyde in the presence of ammonia yields a secondary amine, di-(2-nitro*iso*butyl)amine (I; R = H), also obtained in a purer form when 2-nitropropane reacts with formaldehyde and sodium cyanide. When, in the former mixture, ammonia was replaced by methylamine the *N*-methyl derivative of (I) was produced. Formaldehyde, 2-nitropropane, and *cyclo*hexylamine give N-cyclo*hexyl*-2-*nitro*iso*butylamine*.

IT has been shown (Hirst, Jones, Minahan, Ochynski, Thomas, and Urbanski, *J.*, 1947, 924) that 1-nitropropane reacts with formaldehyde and ammonia yielding polymeric substances. 2-Nitropropane reacts with ammonia and formaldehyde in an analogous manner, but does not yield compounds of high molecular weight; instead, di-(2-nitro*iso*butyl)amine (I; R = H) is produced (cf. Senkus, *J. Amer. Chem. Soc.*, 1946, **68**, 11).

$$NO_2{\cdot}CHMe_2 + 2CH_2O + NH_3 \longrightarrow (NO_2{\cdot}CMe_2{\cdot}CH_2)_2NR \quad (I.)$$

The same substance is formed in better yield if the ammonia is replaced by sodium cyanide, probably as a result of the reactions :

$$CH_2O + NaCN + H_2O \longrightarrow OH{\cdot}CH_2{\cdot}CN + NaOH$$
$$OH{\cdot}CH_2{\cdot}CN + NaOH + H_2O \longrightarrow OH{\cdot}CH_2{\cdot}CO_2Na + NH_3$$

If sodium cyanide is replaced by potassium cyanide, the yield is reduced.

If the ammonia is replaced by methylamine or *cyclo*hexylamine, the product is, respectively, (I; R = CH_3) or *N-cyclo*hexyl-2-nitro*iso*butylamine. All these condensations are similar to those encountered in the Mannich reaction.

Experimental.

Di-(2-nitroisobutyl)amine.—2-Nitropropane (0·2 mol., 17·8 g.) was mixed with 40% formaldehyde (0·4 mol., 30 c.c.) and 28% ammonia (0·2 mol., 12 c.c.). A spontaneous reaction occurred with evolution of heat, and an oily layer separated. After *ca.* 30 minutes the reaction subsided, and the solution was then boiled for an hour. The oil was separated from the cooled solution and purified by washing it with water. It partly crystallised when kept. *Di-(2-nitroisobutyl)amine* (I; R = H), isolated on a tile (yield, 2·4 g.), was recrystallised from alcohol and water; it formed white plates, m. p. 35° [Found : C, 44·1; H, 8·1; N, 19·5; *M* (Rast), 213. $C_8H_{17}O_4N_3$ requires C, 43·8; H, 7·8; N, 19·2%; *M*, 219], soluble in most organic solvents but insoluble in water.

(I; R = H) was prepared in better yield by mixing 2-nitropropane (17·8 g.) with 40% formaldehyde (100 c.c.) and a solution of sodium cyanide (16 g.) in water (50 c.c.). A spontaneous reaction ensued, the temperature increasing by *ca.* 50°. After *ca.* 15 minutes the reaction subsided, and the solution was then boiled for a further 45 minutes. An oily product (7·1 g.) had separated, which solidified on the addition of cold water (150 c.c.). Recrystallised from aqueous alcohol, it had m. p. 35°, undepressed on admixture with the previous sample (Found : N, 19·4%).

The amine (5 g.) was dissolved in hot (*ca.* 100°) 50% sulphuric acid (27 g.); the *hydrogen sulphate* which separated on cooling, crystallised from acetic acid as needles, m. p. 170° (decomp.) (4·1 g.) (Found : C, 29·9; H, 6·5; N, 13·0; S, 9·8. $C_8H_{17}O_4N_3,H_2SO_4$ requires C, 30·3; H, 6·5; N, 13·2; S, 10·1%). It can also be prepared by using 10% sulphuric acid. It is sparingly soluble in cold, but readily soluble in hot water, alcohol, acetone, or acetic acid, and insoluble in ether, benzene, or chloroform.

Adding an excess of hydrogen chloride in alcohol to the amine (3 g.) in ether (30 c.c.) gave an immediate crystalline precipitate of the *hydrochloride* (1·2 g.), m. p. 178° (decomp.) (from acetic acid) (Found : N, 16·0; Cl, 13·8. $C_8H_{17}O_4N_3,HCl$ requires N, 16·0; Cl, 13·9%), also obtained by dissolving the amine in hot aqueous 10% hydrochloric acid.

The amine hydrochloride (1 g.) was dissolved in cold water (20 c.c.) and a 20% solution of sodium nitrite was added. The white precipitate formed was dissolved in ether, washed with 10% sodium carbonate and then with water, and dried (Na_2SO_4). Evaporation left the *nitroso*-compound, which crystallised from ether in needles, m. p. 128° (0·8 g.) (Found : C, 39·3; H, 6·9; N, 22·8. $C_8H_{16}O_5N_4$ requires C, 39·6; H, 6·45; N, 22·6%). It gives a positive Liebermann reaction, and is almost insoluble in water but readily soluble in ether. It dissolved slowly in boiling hydrochloric acid to yield the hydrochloride of (I; R = H) which separated on cooling, m. p. and mixed m. p. 176°. The *N*-nitroso-compound was recovered unchanged after treatment with 10% sodium hydroxide.

N-Methyldi-(2-nitroisobutyl) amine.—2-Nitropropane (6 g.), paraformaldehyde (2 g.), a 30% solution of methylamine (3 c.c.), and water (25 c.c.) were mixed, warmed at 60° for 3 hours, and cooled. The mixture was extracted with ether. Evaporation gave a syrup (7 g.), which was distilled under reduced pressure. Fraction 1 (b.p. 80°/0·02 mm.) crystallised partly when kept; after draining on a tile, 2-nitro-*iso*butyl alcohol m. p. 79°, was obtained (Found : C, 40·1; H, 7·4; N, 11·8. Calc. for $C_4H_9O_3N$: C, 40·3; H, 7·6; N, 11·8%). Fractions II (b. p. 90°/0·02 mm.) and III (b. p. 110°/0·02 mm.) did not crystallise; with hydrochloric acid they formed *N-methyldi-(2-nitroisobutyl)amine hydrochloride*, m. p. 166° (decomp.) (Found : C, 40·2; H, 7·2; N, 15·6; Cl, 13·3. $C_9H_{19}O_4N_3,HCl$ requires C, 40·1; H, 7·4; N, 15·6; Cl, 13·2%).

Keeping the syrupy tertiary amine in methyl iodide gave the crystalline *methiodide* which, when recrystallised from alcohol–ether, had m. p. 169° (Found : C, 32·1; H, 5·9; N, 12·3; I, 36·6. $C_{10}H_{22}O_4N_3I$ requires C, 32·0; H, 5·9; N, 11·2; I, 33·9%).

N-cyclo*Hexyl-2-nitroisobutylamine Hydrochloride.*—2-Nitropropane (3 g.) was warmed with paraformaldehyde (1 g.), *cyclo*hexylamine (1 g.), and water (50 c.c.) at 60° for 1 hour. The product was isolated by extraction with ether. The resultant syrup yielded, with concentrated hydrochloric acid, crystalline N-cyclo*hexyl-2-nitroisobutylamine hydrochloride.* Recrystallised from aqueous alcohol, this had m. p. 201° (Found : C, 50·8; H, 9·1; N, 11·4; Cl, 14·6. $C_{10}H_{20}O_2N_2,HCl$ requires C, 50·7; H, 8·9; N, 11·8; Cl, 15·0%).

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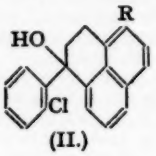
379. *Polycyclic Aromatic Hydrocarbons. Part XXXV. Isomerization in the Perinaphthene Series.*

By G. M. Badger, W. Carruthers, and J. W. Cook.

An example of isomerization in the perinaphthene series, leading to the conversion, by dehydration, of the *methoxy-carbinol* (II; R = OMe) into the *ketone* (VIII) is described. The implications of this in regard to the tautomeric mobility of the perinaphthene system are discussed.

The possibility of tautomerism between six structures in the perinaphthene system (I) * was suggested by Klyne and Robinson (*J.*, 1938, 1991). Although the *reversible* changes which this implies have not yet been realised, the double-bond mobility which is inherent in such a conception was later demonstrated by Fieser and Gates (*J. Amer. Chem. Soc.*, 1940, **62**, 2335), who found, that when the carbinol (II; R = H) was submitted to a series of reactions involving dehydration, reduction, and replacement of the chlorine by a cyano-group, without isolation of intermediates, two products were obtained which were shown to have the structures (IV) and (V). These products must have arisen by a bond rearrangement in the initial product of dehydration, and there was no evidence of the formation of the normal product, unaccompanied by bond-migration. It was suggested that the driving force in the rearrangement was the tendency to conjugation between the chlorophenyl group and a naphthalene system.

(I.)



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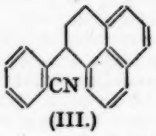

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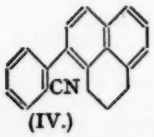

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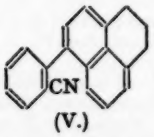

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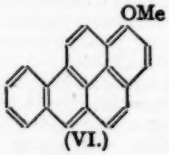


(VI.)

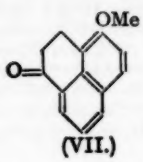
We have now observed a similar rearrangement, which has frustrated an attempt to synthesise 10-methoxy-3 : 4-benzpyrene (VI), one of the (methylated) metabolites of the carcinogenic parent hydrocarbon. By condensation of 4-*methoxyperinaphthan*-1-*one* (VII) with *o*-chlorophenylmagnesium bromide there was obtained 4-*methoxy*-1-*o*-*chlorophenylperinaphthan*-1-*ol* (II; R = OMe). This carbinol, on treatment with a little iodine in boiling light petroleum or with cold dilute methanolic hydrogen chloride, underwent not only dehydration but also rearrangement and demethylation to give the *ketone* (VIII) as the sole product. A Zeisel determination showed the absence of a methoxyl group, and the substance did not decolourise bromine water or dilute permanganate. Moreover, the carbonyl function with an adjacent methylene group was established by preparation of a *semicarbazone*, a 2 : 4-*dinitrophenylhydrazone*, and a *benzylidene* derivative. The formation of such a ketone may be interpreted as dehydration of the carbinol (II; R = OMe) to (IX), followed by rearrangement to (X). (X) would be the ether of an enol, and its hydrolysis and conversion into (VIII) under the experimental conditions used would not be surprising. It is of considerable interest that the ketone (VIII) was the only product formed and that it was not accompanied by compounds of type (XI) structurally analogous to an intermediate leading to one of the compounds (IV) isolated in the example studied by Fieser and Gates (*loc. cit.*).

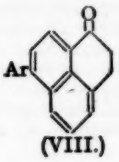
This result supports the conception of Klyne and Robinson (*loc. cit.*) of the tautomeric character of the perinaphthene system, for if (X) and (XI), for example, are regarded as in tautomeric equilibrium then the equilibrium would be disturbed by conversion of (X) into the ketone (VIII), so that ultimately (XI) would be wholly converted into (VIII).

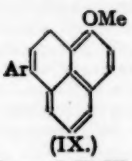
The starting point in the synthesis of the methoxyperinaphthanone (VII) was 2-methoxynaphthalene, which was chloromethylated by a modification of the method of Cook, Downer, and Hornung (*J.*, 1941, 502); the product was condensed with ethyl malonate to give *ethyl*

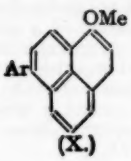
* To avoid anomalies in naming certain derivatives perinaphthene will be numbered as shown in (I). —Ed.

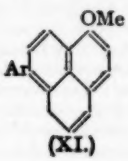
2-methoxy-1-naphthylmethylmalonate. Hydrolysis and decarboxylation then gave β-(2-methoxy-1-naphthyl)propionic acid (XIII). This method represents a considerable improvement on


(VII.)

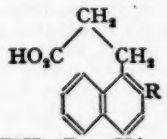

(VIII.)

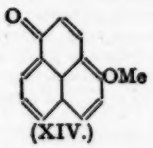

(IX.)
[Ar = C_6H_4Cl]


(X.)


(XI.)

that used by Barger and Starling (*J.*, 1911, 2030) who obtained the same acid, in poor yield, by reduction of the corresponding acrylic acid. For the cyclisation of this acid (XIII) we investigated three methods. With anhydrous hydrogen fluoride (cf. Fieser and Gates, *loc. cit.*), 4-methoxyperinaphthan-1-one (VII) was obtained in good yield, and its structure was confirmed by the preparation of an *oxime* and a *benzylidene* derivative. The same product was also obtained from the acid chloride of (XIII) with stannic chloride. This is of some interest, for it has been found that although the cyclisation of the methoxy-free acid (XII) proceeds normally with hydrogen fluoride to give the colourless perinaphthanone, cyclisation with stannic chloride or aluminium chloride gives the yellow perinaphthenone (XV) (Fieser and Gates, *loc. cit.*; Cook and Hewett, *J.*, 1934, 368). The compound (XV) is basic and readily dissolves in concentrated hydrochloric acid. The ketone (VII) obtained in the present work was yellow, and in view of the above it seemed likely that the colour was due to contamination with some of the dehydrogenated product (XIV). It was, however, not possible to remove the colour, either by extraction of a benzene solution with hydrochloric acid or by chromatography on alumina.


(XII; R = H.)
(XIII; R = OMe.)


(XIV.)

(XV.)

A compound of structure (VII) has already been reported by Barger and Starling (*loc. cit.*) having been obtained, in small yield, by cyclisation of the acid (XIII) with phosphoric oxide. This product was clearly not identical with the ketone described above, and the cyclisation with phosphoric oxide has therefore been re-investigated. The crude product was found to be a complex mixture, and two crystalline products were isolated. One of these has been identified as perinaphthenone (XV), by comparison with an authentic specimen. The formation of this compound requires demethylation and dehydration of (VII), with bond rearrangement. The second crystalline product isolated was apparently identical with the substance isolated by Barger and Starling. Its solubility in hydrochloric acid and its other properties suggest that it is *4-methoxyperinaphthen-1-one* (XIV), and not 4-methoxyperinaphthan-1-one (VII) as suggested by Barger and Starling.

If the explanation which is postulated for the rearrangements discussed above is correct, then it is conceivable that the carbinols which should result from interaction of (VII) with methylmagnesium iodide or 9-anthranylmagnesium bromide would undergo dehydration without rearrangement to give compounds of type (IX). In the latter case it was anticipated that steric inhibition of resonance would prevent true conjugation and hence prevent rearrangement. Attempts to test this hypothesis were unsuccessful. Methylmagnesium iodide reacted with (VII) to give an uncrystallisable oil, and the dehydration product was also an oil. Anthranylmagnesium bromide did not react with the ketone (VII), for, after decomposition with water, only anthracene was isolated.

Experimental.

2-Methoxy-1-chloromethylnaphthalene.—In our hands, the method of Cook, Downer, and Hornung (*loc. cit.*) led to insoluble high-melting material, and a slightly less vigorous method was therefore used. Hydrogen chloride was passed through an ice-cold suspension of paraformaldehyde (18 g.) in glacial acetic acid (250 c.c.), until a clear solution was obtained. A suspension of 2-methoxynaphthalene (45 g.) in glacial acetic acid (400 c.c.) was gradually added to the cold solution, with shaking. After 2 hours at room temperature, the crystalline product was collected and recrystallised from benzene–light

petroleum (b. p. 60—80°). 2-Methoxy-1-chloromethylnaphthalene formed colourless rhombs (40 g.), m. p. 117—120° (decomp.). After further recrystallisation, it had m. p. 122—123° (decomp.) [lit., 120° (decomp.)].

Ethyl 2-Methoxy-1-naphthylmethylmalonate.—2-Methoxy-1-chloromethylnaphthalene (10 g.) in dry benzene (15 c.c.) was added to a solution of ethyl sodiomalonate (from ethyl malonate 10 g., sodium 1·4 g., dry benzene 50 c.c., and absolute ethanol 20 c.c.), and the mixture heated under reflux for 3 hours. The cooled solution was washed with, successively, dilute acid, sodium carbonate solution, and water. The oil obtained after removal of the solvent and the excess of ethyl malonate (b. p. 200—205°/2·5 mm.; 11·9 g.) solidified when cooled in presence of a little alcohol. *Ethyl 2-methoxy-1-naphthylmethylmalonate* formed colourless hexagonal plates, m. p. 56°, from ethanol (Found: C, 69·3; H, 6·9. $C_{19}H_{22}O_5$ requires C, 69·1; H, 6·7%).

β-(2-Methoxy-1-naphthyl)propionic Acid (XIII).—The above ester (11 g.) was hydrolysed by boiling for 2 hours with aqueous alcoholic potassium hydroxide. The *malonic acid* (10 g.) crystallised from water as a colourless micro-crystalline powder, m. p. 174—175° (decomp.) (Found: C, 65·6; H, 4·6. $C_{15}H_{14}O_5$ requires C, 65·7; H, 5·1%). This (9·5 g.) was decarboxylated by heating it at 190° for a few minutes (until evolution of carbon dioxide ceased). The residual oil, crystallised from acetic acid (charcoal), gave β-(2-methoxy-1-naphthyl)propionic acid as colourless flat needles, m. p. 131° (*lit.*, 128°) (Found: C, 73·0; H, 6·0. Calc. for $C_{14}H_{14}O_3$: C, 73·0; H, 6·1%). In a large-scale run, in which the malonic ester was not isolated but was directly hydrolysed and the product decarboxylated, 80 g. of chloromethyl compound gave 72 g. of pure propionic acid, an overall yield of 80%.

Cyclisation with Hydrogen Fluoride.—The above acid (1·5 g.) was left in contact with anhydrous hydrogen fluoride, at room temperature, for 3½ hours. The red solution was poured on ice, and the yellow solid collected and extracted with warm dilute sodium carbonate. No acid was recovered from this extract. The neutral material was dissolved in benzene, and the solution was repeatedly extracted with fresh portions of concentrated hydrochloric acid. The benzene solution remained coloured, and it was accordingly passed through a column of alumina and eluted with benzene. No evidence was obtained that the yellow colour was due to an impurity. Evaporation of the benzene gave *4-methoxyperinaphthan*-1-one (VII) as yellow plates, m. p. 65° (1·1 g., 80%) (Found: C, 79·4; H, 5·7. $C_{14}H_{12}O_2$ requires C, 79·2; H, 5·7%). The *oxime*, prepared by the method of Cook, Hewett, and Lawrence (*J.*, 1936, 79), formed pale yellow needles, m. p. 157—159° (decomp.), from ethanol (Found: C, 73·8; H, 5·6; N, 6·0. $C_{14}H_{13}O_2N$ requires C, 74·0; H, 5·7; N, 6·2%).

The *benzylidene* derivative was prepared by treating a mixture of the ketone (0·5 g.) and benzaldehyde (1 g.) in ethanol (5 c.c.) with potassium hydroxide (1 g.) in ethanol (10 c.c.). After 20 hours at room temperature, the mixture was acidified with acetic acid, diluted with water, and extracted with benzene. Removal of the benzene gave an oil which deposited a solid material (0·15 g.) when treated with alcohol and, after crystallisation from benzene–light petroleum (b. p. 60—80°), this was obtained as orange-red prisms, m. p. 172—173° (Found: C, 84·2; H, 5·7. $C_{21}H_{16}O_2$ requires C, 84·0; H, 5·4%).

Cyclisation with Stannic Chloride.—A cooled mixture of the methoxynaphthylpropionic acid (XIII) (10 g.) and dry thiophen-free benzene (100 c.c.) was treated with phosphorus pentachloride (8 g.). After 1 hour at room temperature, the mixture was heated on the steam-bath for 5 minutes. After cooling in ice, the mixture was treated with stannic chloride (10 c.c.) in dry thiophen-free benzene (100 c.c.). The reaction was allowed to proceed for 4 hours, after which the product was hydrolysed with ice and hydrochloric acid, and the benzene layer separated. After being washed with concentrated hydrochloric acid, sodium carbonate solution, and water, it was dried and evaporated. Methoxyperinaphthanone (8 g.), m. p. 65°, identical (mixed m. p.) with the product obtained as above, was obtained by recrystallisation from light petroleum. The identity of the products was confirmed by comparison of the oximes.

Cyclisation with Phosphoric Oxide.—Methoxynaphthylpropionic acid (2 g.) in dry benzene (20 c.c.) was treated with phosphoric oxide (10 g.), and the mixture heated for 2 hours on the water-bath and then kept overnight at room temperature. After treatment with ice, the benzene solution was separated, washed with sodium carbonate (0·6 g. of acid recovered) and then with water, and dried. Removal of the solvent gave a dark oil which deposited some crystals when kept. Recrystallisation from benzene–light petroleum (60—80°) gave *4-methoxyperinaphthen*-1-*one* (XIV) as orange yellow needles, m. p. 142—143° (Barger and Starling give m. p. 135°) (Found: C, 79·9; H, 4·9. $C_{14}H_{10}O_2$ requires C, 80·0; H, 4·8%). The oil remaining after the removal of the crystalline material was passed through a column of alumina. Several bands were obtained. A pale yellow band having a bright yellow fluorescence in ultra-violet light was removed by elution with benzene; after the solvent had been removed, the yellow residue (10 mg.) was further recrystallised from light petroleum (60—80°) from which yellow needles, m. p. 150°, separated; this was perinaphthenone (XV) (mixed m. p., 150—152°, with an authentic specimen, m. p. 153°). The other bands of the chromatogram yielded small amounts of uncrystallisable oils, and were not further examined.

4-Methoxy-1-o-chlorophenylperinaphthan-1-ol (II; R = OMe).—A solution of 4-methoxyperinaphthan-1-one (12 g.) in dry thiophen-free benzene (200 c.c.) was slowly added to a Grignard solution, from magnesium (2·3 g.) and *o*-chlorobromobenzene (18 g.) in ether (200 c.c.) with constant stirring. A yellow solid separated. After being kept overnight at room temperature, the mixture was heated under reflux for 1 hour and then decomposed with aqueous ammonium chloride. The ethereal solution was separated and washed with dilute sodium hydroxide until the washings were no longer red, and then with water. The oil remaining after removal of the ether was steam-distilled to remove excess of *o*-chlorobromobenzene. The resulting oil deposited a yellow solid (5 g.) when triturated with light petroleum. After crystallisation from methanol (charcoal) and then from benzene–light petroleum (b. p. 60—80°), *4-methoxy-1-o-chlorophenylperinaphthan-1-ol* was obtained as colourless prisms, m. p. 151—152° (Found: C, 74·1; H, 5·5; OMe, 9·6. $C_{20}H_{17}O_2Cl$ requires C, 73·9; H, 5·2; OMe, 9·6%).

7-o-Chlorophenylperinaphthan-1-one (VIII).—A mixture of the above carbinol (1 g.) and iodine (10 mg.) in light petroleum (b. p. 80—100°) was heated under reflux for ½ hour. The cooled solution was washed with dilute sodium thiosulphate and then with water and evaporated. Crystallisation from

ethanol gave 7-o-*chlorophenylperinaphthan*-1-*one* (0·7 g.) as pale yellow prisms, m. p. 109—110° (Found: C, 77·6; H, 4·5; OMe, 0·0. $C_{19}H_{13}OCl$ requires C, 77·9; H, 4·4; OMe, 0·0%). The same ketone was obtained in quantitative yield when the carbinol (0·5 g.) in methanol (5 c.c.) and benzene (1 c.c.) was treated with a saturated solution of methanolic hydrogen chloride (1 c.c.), for 24 hours. The 2 : 4-*dinitrophenylhydrazone* formed soft deep-red needles, m. p. 228° (decomp.), from glacial acetic acid (Found: C, 63·2; H, 3·7 $C_{25}H_{17}O_4N_4Cl$ requires C, 63·5; H, 3·6%). The *semicarbazone* crystallised from ethanol in clusters of bright yellow needles which sintered at 220° and finally melted with decomposition at 236° (Found: C, 68·9; H, 4·8. $C_{20}H_{16}ON_3Cl$ requires C, 69·2; H, 4·6%). The *benzylidene* derivative crystallised out when a mixture of the ketone (0·3 g.), benzaldehyde (1 g.), potassium hydroxide (1 g.), and ethanol (15 c.c.) was set aside for 24 hours at room temperature. After recrystallisation from xylene, it formed bright yellow prisms, m. p. 225° (Found: C, 81·9; H, 4·7. $C_{26}H_{17}OCl$ requires C, 81·9; H, 4·5%).

One of us (G. M. B.) has been working with an I.C.I. Research Fellowship, and we are also indebted to the University for a Maintenance Allowance (to W. C.). Microanalyses have been carried out by Mr. J. M. L. Cameron.

UNIVERSITY OF GLASGOW. [*Received, October 13th*, 1948.]

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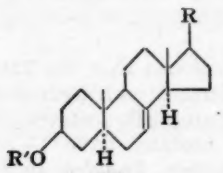
380. *The Application of the Method of Molecular Rotation Differences to Steroids. Part X.* "β-*Dihydroergosterol.*"

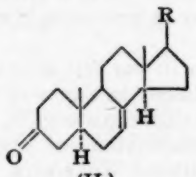
By D. H. R. BARTON, J. D. COX, and N. J. HOLNESS.

Isomerisation of "α"-dihydroergosteryl acetate gives an inseparable mixture, formerly designated "β-dihydroergosteryl acetate," of ergosta-8(14) : 22(23)-dien-3(β)-yl and ergosta-14(15) : 22(23)-dien-3(β)-yl acetate in equimolecular amounts. Hydrogenation of *iso*ergosterone in neutral solution affords a complex mixture of *ergost*-22(23)-*ene*, *coproergost*-22(23)-*en*-3-*one*, *ergost*-22(23)-*en*-3-*one*, and *ergosta*-4(5) : 22(23)-*dien*-3-*one* (*brassicastadienone*), from which further transformation products have been prepared. The changes in molecular rotation associated with the hydrogenation of a 22(23)-ethylenic linkage are discussed.

THE preparation of "β-dihydroergosteryl acetate" by isomerisation of "α"-dihydroergosteryl acetate (I; R = C_9H_{17}, R′ = Ac) with dry hydrogen chloride was described first by Heilbron, Johnstone, and Spring (*J.*, 1929, 2248). Another route to this substance was reported later by Dithmar and Achtermann (*Z. physiol. Chem.*, 1932, **205**, 55) who isomerised "α"-ergostadienone (II; R = C_9H_{17}) with hydrogen chloride and reduced the product, "β-ergostadienone," with sodium and alcohol to "β-dihydroergosterol." *

We have repeated the preparation of "β-dihydroergosterol" and its derivatives according to the directions of Heilbron, Johnstone, and Spring, and have obtained this substance with


(I.)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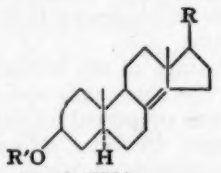
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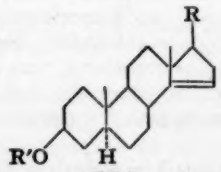
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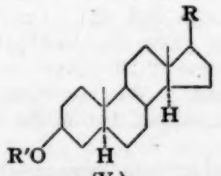
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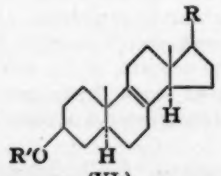

(VI.)

constants in fair agreement (Table I) with those recorded previously. We have carried out this preparation on several occasions and, provided that the "α"-dihydroergosteryl acetate used was entirely free from ergosteryl acetate, we have always been able to repeat exactly the physical constants we record in Table I (see also Experimental section).

* Dithmar and Achtermann actually called their product "dihydroergosterol III," but they considered it to be identical with the substance prepared earlier by Heilbron and his collaborators.

TABLE I.*

	Alcohol.		Acetate.		Benzoate.		Ketone.	
	m. p.	$[\alpha]_D$.	m. p.	$[\alpha]_D$.	m. p.	$[\alpha]_D$.	m. p.	$[\alpha]_D$.
Heilbron, Johnstone, and Spring (*loc. cit.*)	124°	− 7·0° †	108—109°	−25·2° †	—	—	125°	—
Dithmar and Achtermann (*loc. cit.*)	122	−16·7	108	−25·3	—	—	114	−5°
This paper	116	− 9	104·5	−17	116°	−8°	125—126	+4

* All rotations in this paper are for chloroform solutions and the Na_D line, unless specified to the contrary.

† For the 5461 A. line.

It is generally considered (Sobotka, "The Chemistry of the Sterids," Baillière, Tindall, and Cox, 1938) that "β-dihydroergosterol" is represented by the formula (IV; R = C_9H_{17}, R′ = H) and is, in fact, the 22 : 23-dehydro-derivative of "β"-ergostenol (IV; R = C_9H_{19}, R′ = H) (cf. W. Bergmann and Klacsmann, *J. Org. Chem.*, 1948, **13**, 21). Now in Part II of this series (*J.*, 1946, 512) we pointed out that this view was incompatible with both the chemical and the optical-rotation evidence and suggested that "β-dihydroergosterol" might be a mixture containing a proportion of the strongly lævorotatory compound ergosta-5(6) : 22(23)-dien-3(β)-ol (brassicasterol).

Whereas "β"-ergostenol is hydrogenated to ergostanol (V; R = C_9H_{19}, R′ = H) in almost quantitative yield "β-dihydroergosteryl acetate" was said to afford "α"-ergostenyl acetate (III; R = C_9H_{19}, R′ = Ac) (Heilbron, Johnstone, and Spring, *loc. cit.*). In our hands catalytic hydrogenation of "β-dihydroergosteryl acetate" in acid solution gave a mixture of equal amounts of ergostanyl and "α"-ergostenyl acetate. Our previous suggestion with regard to a Δ^5-contaminant was based on the claims of Wieland and Benend (*Ber.*, 1942, **75**, 1708) that the nuclear olefinic linkages in zymosterol and zymostenol, now known to be (VI; R = C_8H_{15}, R′ = H) and (VI; R = C_8H_{17}, R′ = H), respectively (this vol., p. 214), could be in part rearranged to the Δ^5-position. These claims have now been withdrawn (Wieland and Gornhardt, *Annalen*, 1947, **557**, 248) and, indeed, oxidation of "β-dihydroergsterol" by the Oppenauer method, followed by chromatography, failed to reveal any trace of the Δ^4-3-one which might have been expected. The Δ_3 value (Table II) of +52°, for "β-ergostadienone" is in fair agreement with the normal one of +73° for *trans*-(A/B)-3(β)-stanols (*J.*, 1948, 783) whereas the value for the change to a Δ^4-3-one is very large (+511°). All attempts to show, either by fractional crystallisation of the acetate and benzoate or by chromatography of the acetate, that "β-dihydroergosterol" was a mixture, failed. Although there was slight evidence for heterogeneity in the latter experiments, it was quite impossible to obtain any clear-cut resolution.

At this stage of the investigation it was felt desirable to confirm that the 22(23)-olefinic linkage in the side-chain was not altered in any way by treatment with hydrogen chloride. This view was supported by the facts that ergosteryl B_1 and ergosteryl B_3 acetates, prepared by the hydrogen chloride induced isomerisation of ergosteryl acetate, gave (−)-methyl*iso*propylacetaldehyde on ozonolysis (Guiteras, Nakamiya, and Inhoffen, *Annalen*, 1932, **494**, 116) and that the ergosteryl acetate–maleic anhydride adduct was unchanged by treatment with hydrogen chloride (Inhoffen, *ibid.*, 1934, **508**, 81). On ozonolysis (see Experimental section) "β-dihydroergosteryl acetate" also gave (−)-methyl*iso*propylacetaldehyde. Furthermore stigmasteryl acetate, which has the same 22(23)-ethylenic linkage as ergosterol, was unchanged by treatment with hydrogen chloride. We conclude, therefore, that the side-chain of "α"-dihydroergosteryl acetate is not altered during the conversion into "β-dihydroergosteryl acetate."

The nature of "β-dihydroergosteryl acetate" was finally elucidated by a study of the product of its hydrogenation in neutral solution. In ethyl acetate as solvent and in presence of a not too active platinum catalyst "β-dihydroergosteryl acetate" afforded, in high yield, a substance, m. p. 93·5—94·5°, $[\alpha]_D$ +6°, whose constants were unchanged on recrystallisation. This material gave no depression in m. p. on admixture with an equimolecular mixture, m. p. 93·5—94·5°, $[\alpha]_D$ +6°, of "α"- and "β"-ergostenyl acetate prepared either by isomerisation of "α"-ergostenyl acetate by hydrogen chloride (Reindel, Walter, and Rauch, *ibid.*, 1927, **452**, 34; Reindel and Walter, *ibid.*, 1928, **460**, 212; cf. Hart, Speer, and Heyl, *J. Amer. Chem. Soc.*, 1930, **52**, 2016) or by acetylation of a mixture of equal parts of "α"- and "β"-ergostenol. In

view of the origin of this complex, which it is impossible to resolve by crystallisation, we propose for it the name " αβ-ergostenyl acetate." The acetate from the hydrogenation experiment was converted into the mixed benzoates which by fractional crystallisation afforded both " α "- and " β "-ergostenyl benzoate (cf. Heilbron and Wilkinson, *J.*, 1932, 1708). All this evidence is conclusive that the " β-dihydroergosteryl acetate " hydrogenation product must be " αβ-ergostenyl acetate." In so far as the previous studies in this series have established that hydrogenation in neutral solution using a ***platinum*** catalyst does not lead to rearrangement, the experiments are proof that the so-called " β-dihydroergosterol " is an inseparable equimolecular mixture of ergosta-8(14) : 22(23)-dien-3(β)-ol (III; R = C_9H_{17}, R′ = H) and ergosta-14(15) : 22(23)-dien-3(β)-ol (IV; R = C_9H_{17}, R′ = H). This view is confirmed by consideration of the optical-rotation evidence discussed in detail below, and is in agreement with the behaviour of " β-dihydroergosteryl acetate " on hydrogenation in acid solution (see above).

In Part II of this series (*J.*, 1946, 512) the changes in molecular rotation associated with the reduction of a 22(23)-ethylenic linkage were surveyed and a mean value of +61° was found. This value, which is derived from nuclear substituted substances where " vicinal action " (*J.*, 1948, 783) might be expected and which relates to varying substituents at the 24-position where again " vicinal action " is possible, received apparent confirmation from the rotations recorded for " α "-dihydroergosterol and for " γ "-ergostenol (Table II) where the mean Δ value is +67°. When the latter value is used, the calculated molecular rotations (Table II) for " β-dihydroergosterol," on the basis of the composition proved above, are still not in good agreement with those observed, though the discrepancies are now only *ca.* 8° in specific rotation compared with *ca.* 18° for the previously recorded data (compare Part II, *J.*, 1946, 512). In order to resolve this discrepancy, which is outside the limits of experimental error, the preparation of compounds of the ergostane series containing a saturated nucleus and a single ethylenic linkage at the 22(23)-position, was undertaken. These substances should, according to our previous studies (*J.*, 1948, 783), be entirely free from any suspicion of " vicinal action " and thus should give the required Δ values without ambiguity.

TABLE II.

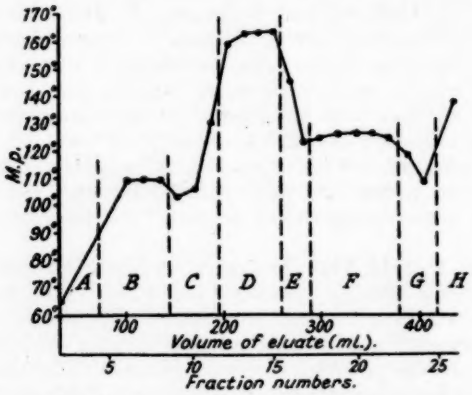
Substance.	$[M]_D$. Alcohol.	Acetate.	Benzoate.	Ketone.	Ref.
" α "-Dihydroergosterol	−76°	−88°	− 50°	+ 8°	1
" γ "-Ergostenol	− 8	−18	+ 10	+ 88	2
(From above : mean Δ = + 67°)	+68	+60	+ 60	+ 80	—
" α "-Ergostenol	+44	+ 4	± 0	+119	2
" β "-Ergostenol	+88	+58	+116	+159	2
Mean	+66	+31	+ 58	+139	—
" β "-Dihydroergosterol :					
Calculated using Δ = + 67°	− 1	−36	− 9	+ 72	—
Calculated using Δ = + 103° *	−37	−72	− 45	+ 36	Exptl.
" β "-Dihydroergosterol :					
Observed rotations	−36	−75	− 40	+ 16	Exptl.

* See Table IV. The mean Δ value includes the data for ergost-22(23)-ene (Exptl.) but excludes the value derived from coproergostan-3-one. References : 1, *J.*, 1948, 1354; 2, *J.*, 1948, 783.

When ergosterone (VII; R = C_9H_{17}) is treated with hydrogen chloride it gives *iso*-ergosterone (VIII; R = C_9H_{17}) from which the required compounds were readily prepared. Partial hydrogenation of *iso*ergosterone in neutral solution until the uptake of hydrogen corresponded to 1·3—1·4 equivalents furnished a complex mixture of products which, on chromatography over alumina, afforded the results shown in the figure.

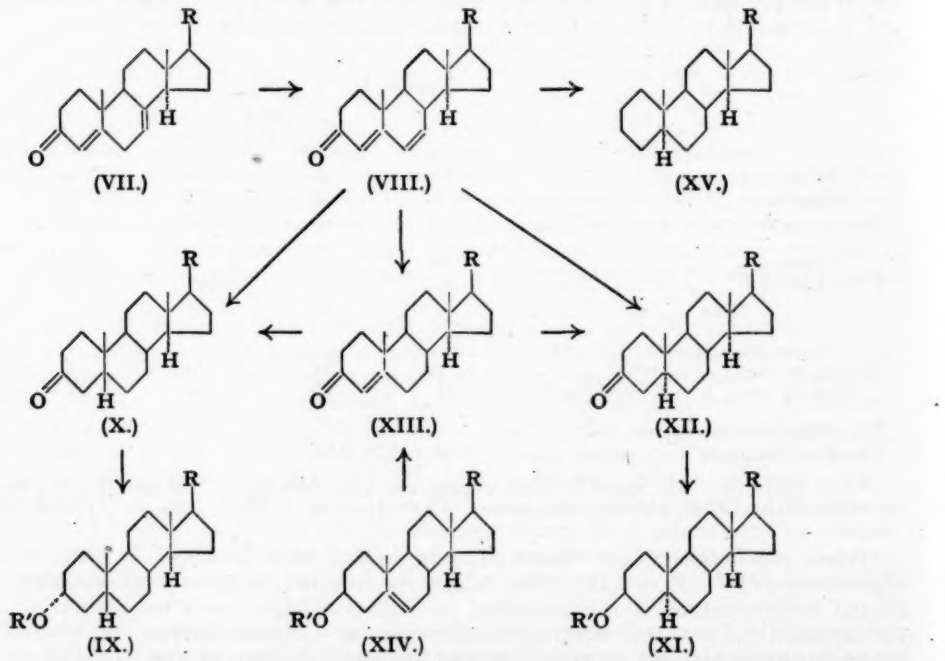
The first fraction (*A*), which was very easily eluted from the column, is discussed further below. Fraction (*B*) gave a pure ketone, m. p. 110·5°, which analysed for $C_{28}H_{46}O$ and showed no absorption in the ultra-violet. On complete hydrogenation in neutral solution this ketone furnished coproergostan-3(α)-ol (IX; R = C_9H_{19}, R′ = H), with only a trace of the digitonin-precipitable 3(β)-isomer. These observations show that ketone (*B*) must be a derivative of coproergostane and thus must be either coproergost-6(7)-en-3-one or coproergost-22(23)-en-3-one. Now the 22(23)-ethylenic linkage is reduced only slowly by hydrogenation in neutral solution,

whereas the hydrogenation of *iso*ergosterone proceeds with great rapidity (see Experimental section). We formulate ketone (*B*) therefore as *coproergost*-22(23)-*en*-3-*one* (X; R = C_9H_{17}).



Fraction numbers.	Elutriant.		Fraction numbers.	Elutriant.	
1— 4	Benzene	A	16—17	Benzene	E
5— 8	Benzene	B	18—22	90 Benzene : 10 Ether	F
9—11	Benzene	C	23—24	70 Benzene : 30 Ether	G
12—15	Benzene	D	25—26	Ether	H

Reduction with sodium and *n*-propanol gave *coproergost*-22(23)-*en*-3(α)-*ol* (IX; R = C_9H_{17}; R′ = H) further characterised as the *acetate*, *acetate dibromide*, and *benzoate*. Fraction (*D*) on



recrystallisation furnished a pure ketone, m. p. 165·5°, also $C_{28}H_{46}O$, which showed no absorption in the ultra-violet. On complete hydrogenation in neutral solution this ketone afforded ergostan-3(β)-ol (XI; R = C_9H_{19}, R′ = H) with only a trace of the non-digitonin-precipitable isomer. Ketone (*D*) must therefore be a derivative of ergostane and accordingly is to be formulated as *ergost*-22(23)-*en*-3-*one* (XII; R = C_9H_{17}). Reduction with sodium and *n*-propanol gave *ergost*-22(23)-*en*-3(β)-*ol* (XI; R = C_9H_{17}, R′ = H) further characterised as the *acetate*, *acetate dibromide*, and *benzoate*. Ketone (*D*) bears the same relation to ketone (*B*) as

cholestanone does to coprostanone; this is borne out by the comparative data shown in Table III.

TABLE III.

	$C_{28}H_{46}O$.			$C_{27}H_{46}O$.		
	(i) Ketone (*B*).	(ii) Ketone (*D*).		(i) Copro-stanone.	(ii) Chol-estanone.	
$[M]_D$	−4°	+24°		+146°	+162°	
(i) − (ii)		−28°			−16°	
M. p.	110·5°	165·5°		64°	128°	
(i) − (ii)		−55°			−64°	
Main product of Na–*n*-PrOH reduction...	3(α)-ol	3(β)-ol		3(α)-ol	3(β)-ol	
Chromatographic behaviour	(i) Eluted before (ii)			(i) Eluted before (ii)		

Fraction (*F*) gave a pure ketone, m. p. 127°—128°, which analysed as $C_{28}H_{44}O$ and showed a strong band at 242 mμ, ε 18,200. From these facts and its marked dextrorotation it must be *ergosta*-4(5) : 22(23)-*dien*-3-*one* (XIII; R = C_9H_{17}). Now the investigations of Fernholz and Stavely (*J. Amer. Chem. Soc.*, 1939, **61**, 142; 1940, **62**, 1875) have shown that the naturally occurring brassicasterol is best represented as ergosta-5(6) : 22(23)-dien-3(β)-ol (XIV; R = C_9H_{17}, R′ = H), so that it should give ketone (*F*) on oxidation by the Oppenauer method. Through the courtesy of Dr. H. E. Stavely (Squibb Institute for Medical Research) who kindly supplied us with a specimen of brassicasterol we were able to show that this is indeed the case. Partial hydrogenation of ketone (*F*) in neutral solution afforded, on chromatography, ketones (*B*) and (*D*) and thus confirmed unambiguously the formulæ ascribed above to the latter ketones.

Fractions (*C*) and (*E*) were combined and again chromatographed over alumina to give ketones (*B*), (*D*), and (*F*), but no trace of any other ketone. Fractions (*G*) melted unsharply even after repeated crystallisation, and were probably mixtures of ketone (*F*) with unchanged *iso*ergosterone. Chromatography of a specimen of *iso*ergosterone which had been hydrogenated to less than one equivalent of hydrogen uptake confirmed that unchanged *iso*ergosterone separated in the chromatogram after ketone (*F*).

Fraction (*A*) consisted of an oily mixture of hydrocarbons which melted unsharply. On treatment with bromine it afforded a crystalline *dibromide* from which, by debromination, a homogeneous mono-olefinic hydrocarbon, $C_{28}H_{48}$, was prepared. The latter product is formulated as *ergost*-22(23)-*ene* (XV; R = C_9H_{17}) since it gave ergostane (XV; R = C_9H_{19}) on hydrogenation in neutral solution and had almost the same molecular rotation as ergost-22(23)-en-3(β)-ol (XI; R = C_9H_{17}, R′ = H) (see Barton and Klyne, *Chem. and Ind.*, 1948, 755T).

Fraction (*H*), which melted unsharply, was resolved by the digitonin method into impure coproergost-22(23)-en-3(α)-ol (IX; R = C_9H_{17}, R′ = H) and ergost-22(23)-en-3(β)-ol (XI; R = C_9H_{17}, R′ = H).

The molecular rotations and Δ values for the compounds prepared above are summarised in Table IV and compared with the appropriate standard values. It will be seen that an isolated

TABLE IV.

Substance.	$[M]_D$. Alcohol.	Acetate.	Benzoate.	Ketone.	Δ_1.	Δ_2.	Δ_3.	Refs.
Ergostan-3(β)-ol	+ 60°	+ 27°	+ 66°	+132°	−33°	+ 6°	+72°	1, Exptl.
Ergost-22(23)-en-3(β)-ol	− 40	− 75	− 40	+ 28	−35	± 0	+68	Exptl.
Δ (from above)	+100	+102	+106	+104	—	—	—	—
Coproergostan-3(α)-ol	+ 93 *	+173	—	+115 *	+80	—	+22	2, 3, Exptl.
Coproergost-22(23)-en-3(α)-ol	− 16	+ 71	+ 45	− 4	+87	+61	+12	Exptl.
Δ (from above)	+109	+102	—	+119	—	—	—	—

* Calculated from the corresponding coprostan-3(α)-ol derivatives by subtraction of 31 units—the standard difference in $[M]_D$ between cholestanol and ergostanol derivatives.

References: 1, *J.*, 1948, 1354; 2, *J.*, 1949, 337; 3, *J.*, 1946, 1116.

ethylenic linkage in the side-chain does not exert "vicinal action" at the 3-position. This is in agreement with our previous study of the subject (Barton and Cox, *J.*, 1948, 783). The data do, however, reveal a marked difference between the Δ values for side-chain reduction of the 22(23)-ethylenic linkage in "α"-dihydroergosterol (Table II),* as compared with the

* This effect is also shown by other compounds having 7(8)- and 22(23)-ethylenic linkages. See this vol., p. 337.

nuclearly saturated compounds described in this paper. Such " vicinal action," transmitted through four saturated carbon atoms, would not have been expected from our previous studies (Barton and Cox, *loc. cit.*) although these have not hitherto included diethylenic derivatives. The case is noteworthy because in " β-dihydroergosterol " (see above) it appears that the ethylenic linkages at positions 8(14) and 14(15), which are separated by three saturated carbon atoms from position 22, do not affect the Δ value for the reduction of the 22(23)-bond. It should also be pointed out that the Δ_2 value for " β-dihydroergosterol " is in exact agreement with that expected for a mixture of the composition found.

Experimental.

The substances whose rotations are listed below were dried in a vacuum at 20° below their m. p.s or at 120°, whichever was the lower temperature. All rotations are for the Na_D line and in chloroform solution, unless specified to the contrary. The measurements were made at room temperature which varied from 15° to 25°.

In order to improve the accuracy of the rotation measurements, most readings were taken using 1-dm. macro-tubes. Values obtained using a 1-dm. micro-tube have this fact indicated after each individual rotation. All values of $[\alpha]_D$ have been approximated to the nearest degree as in previous parts of this series. For the calculations the specific rotations at *c*, 2·00, or at the nearest concentrations to this at which measurements were made, have been taken as the most suitable. In no case, however, was there any marked variation of specific rotation with concentration.

Acetylations were carried out, unless specified to the contrary, by heating the substance under reflux with acetic anhydride for 30 minutes, and benzoylations by the usual pyridine procedure, the reactants being left for 24 hours at room temperature to complete reaction. Alkaline hydrolyses were effected by using several equivs. of potassium hydroxide and heating the reactants under reflux for 30 minutes in methanolic or dioxan–methanolic solution depending upon the solubility of the ester. Oppenauer oxidations were performed under the normal conditions (Barton and Jones, *J.*, 1943, 599), except that it was found advantageous to use only half the amount of acetone there specified and to heat the mixtures under reflux for only 4 hours instead of the usual 16 hours. It was found that the use of resublimed aluminium *tert.*-butoxide is not essential, and material crystallised from benzene was employed. When the chromatographic technique was used, the usual precautions were taken (see Barton and Jones, *loc. cit.*). M. p.s are uncorrected.

" *β-Dihydroergosteryl Acetate.*"—6-G. portions of carefully purified " α "-dihydroergosteryl acetate (for prep. see *J.*, 1948, 1354) were dissolved in 100 ml. of dry chloroform and treated with dry hydrogen chloride at 0° for 1 hour. The reaction product was worked up according to the directions of Heilbron, Johnstone, and Spring (*J.*, 1929, 2248) and on recrystallisation from ethanol gave " β-dihydroergosteryl acetate," m. p. 104·5°, $[\alpha]_D$ −17° (*c*, 3·74), −17° (*c*, 2·85), −17° (*c*, 0·70), $[M]_D$ −75°, in the form of long needles. Repeated crystallisation did not change the m. p. or rotation. There was no absorption in the ultra-violet.

On one occasion a specimen of " α "-dihydroergosteryl acetate containing, from the absorption spectrum, 8% of ergosteryl acetate, was used for the preparation. On being worked up as above it was not possible by fractional crystallisation to obtain reproducible constants. The m. p. rose very slowly from 106° to 107°, whilst the rotation eventually attained $[\alpha]_D$ −34° (*c*, 1·67; micro-tube). The absorption spectrum of this material showed a weak maximum at 248 mμ, $E^{1\%}_{1\,cm.}$ 40, corresponding to about 15% of a conjugated diene with the ethylenic linkages distributed between two rings (probably ergosteryl B_2 acetate), and confirmed that a contaminant was concentrated by recrystallisation. This material was dissolved in xylene and treated at the b. p. for 6 hours with an excess of maleic anhydride. After the mixture had been worked up in the customary manner " β-dihydroergosteryl acetate," $[\alpha]_D$ −18° (*c*, 0·67; micro-tube), was isolated, identical with the material described above. These experiments illustrate the importance of the careful purification of the " α "-dihydroergosteryl acetate before isomerisation.

" *β-Dihydroergosterol.*"—This was prepared from the above acetate by alkaline hydrolysis in the usual way. Recrystallised from methanol it had m. p. 116°, $[\alpha]_D$ −9° (*c*, 3·38), $[M]_D$ −36°. There was no absorption in the ultra-violet.

" *β-Dihydroergosteryl Benzoate.*"—The above alcohol was benzoylated, and the benzoate recrystallised from ethyl acetate–methanol; this *compound* had m. p. 116°, $[\alpha]_D$ −9° (*c*, 1·78; micro-tube), −8° (*c*, 1·64; micro-tube), $[M]_D$ −40°, unchanged on repeated recrystallisation (Found: C, 83·8; H, 9·9. $C_{35}H_{50}O_2$ requires C, 83·6; H, 10·0%). Alkaline hydrolysis furnished " β-dihydroergosterol," m. p. 117°, $[\alpha]_D$ −9° (*c*, 2·04), which on acetylation by the pyridine method gave " β-dihydroergosteryl acetate," m. p. 104·5°, $[\alpha]_D$ −18° (*c*, 1·38; micro-tube), both compounds being apparently identical with those described above.

" *β-Ergostadienone.*"—3 G. of " β-dihydroergosterol " were oxidised by the Oppenauer procedure, and the reaction product was chromatographed over alumina (12 fractions). Only one band was observed, although Δ^4-3-ones are normally separated very efficiently by this process (Barton and Jones, *loc. cit.*; cf. below) from the corresponding stanones. Except the first three (gummy) fractions, all were combined and recrystallised from ethanol to give " β-ergostadienone," m. p. 125—126°, $[\alpha]_D$ +4° (*c*, 1·19), $[M]_D$ +16°. The 2 : 4-*dinitrophenylhydrazone*, prepared in the usual way, gave only a broad orange band on chromatography over alumina and no trace of a red band such as would correspond to any Δ^4-3-one present as contaminant; after slow recrystallisation from chloroform–methanol it had m. p. 203° (Found: N, 9·5. $C_{34}H_{48}O_4N_4$ requires N, 9·7%).

Ozonolysis of " *β-Dihydroergosterol.*"—1·0 G. of " β-dihydroergosterol " was suspended in AnalaR acetic acid (30 ml.), and ozonised oxygen was bubbled through the liquid for 30 minutes (all steroid had

passed into solution after 15 minutes). The solution was poured into water (30 ml.), and the mixture was warmed for 10 minutes with occasional addition of zinc dust. Finally the liquid was distilled, and to the first 20 ml. of aqueous distillate was added 1 g. of semicarbazide hydrochloride, followed by sufficient sodium hydrogen carbonate to render the solution only slightly acid. The mixture was set aside at 0° for 18 hours. The precipitate was filtered off and recrystallised from benzene–light petroleum. The product had m. p. 129·5°, $[\alpha]_D$ −52° (*c*, 1·30; micro-tube; in ethanol). Guiteras, Nakamiya, and Inhoffen (*Annalen*, 1932, **494**, 116) give for (−)-methyl*iso*propylacetaldehyde semicarbazone, m. p. 129—130°, $[\alpha]_D$ −52° (in ethanol).

Hydrogenation of "β-Dihydroergosteryl Acetate" in Acid Solution.—(i) 130 Mg. of "β-dihydroergosteryl acetate" were dissolved in 1 : 1 ether–acetic acid (60 ml.) and hydrogenated during 7 hours in presence of 100 mg. of platinum oxide catalyst. The product was recrystallised from ethanol to give ergostanyl acetate, m. p. 143°, $[\alpha]_D$ +6° (*c*, 1·30; micro-tube), in 25% yield.

(ii) 150 Mg. of "β-dihydroergosteryl acetate" were hydrogenated as described above. The crude product, m. p. 110—120°, was crystallised once to give (*a*) 60 mg., m. p. 130—133°, $[\alpha]_D$ +5° (*c*, 2·49; micro-tube), and complete evaporation of the mother-liquors of this crystallisation afforded (*b*) 90 mg., m. p. *ca.* 100°, $[\alpha]_D$ +3° (*c*, 1·83; micro-tube). These m. p.s and rotations accord best with those for mixtures of ergostanyl acetate, m. p. 144°, $[\alpha]_D$ +6° (see below), and "α"-ergostenyl acetate, m. p. 109°, $[\alpha]_D$ +1° (*J.*, 1948, 783). The ratio of the two, calculated from the observed rotations, is about 1 : 1.

(iii) 160 Mg. of "β-dihydroergosteryl acetate" were hydrogenated as described above and the crude product was treated by the Anderson–Nabenhauer procedure (*J. Amer. Chem. Soc.*, 1924, **46**, 1957) to remove unsaturated material. In this way 80 mg. (50%) of ergostanyl acetate, m. p. 144°, $[\alpha]_D$ +6° (*c*, 1·80; micro-tube), were recovered. Again this corresponds to a 1 : 1-mixture of ergostanyl and "α"-ergostenyl acetates.

Hydrogenation of "β-Dihydroergosteryl Acetate" in Neutral Solution.—220 Mg. of "β-dihydroergosteryl acetate" in ethyl acetate (60 ml.) were shaken with 200 mg. of used platinum catalyst in an atmosphere of hydrogen for 27·5 hours. The product, recrystallised from methanol, melted constantly at 93·5—94·5° and had $[\alpha]_D$ +6° (*c*, 0·68). A mixed m. p. with the "αβ-ergostenyl acetate" complex, m. p. 93·5—94·5° (see below), also melted sharply at 93·5—94·5°. The hydrogenation product was hydrolysed and the resulting alcohol mixture benzoylated. The mixed benzoates were crystallised from chloroform–methanol till the m. p. reached 150°. A mixed m. p. with almost pure "β"-ergostenyl benzoate, m. p. 154°, prepared as below, gave m. p. 151°. The combined mother-liquors from the crystallisation of the mixed benzoates were concentrated, and successive crops of crystals removed. The last two crops, m. p. 98—100°, were recrystallised several times from chloroform–methanol to give "α"-ergostenyl benzoate, m. p. 110—111·5°; the mixed m. p. with an authentic specimen, m. p. 112—112·5° (*J.*, 1948, 783), was 110—111·5°.

Rearrangement of "α"-Ergostenyl Acetate.—2 G. of "α"-ergostenyl acetate, m. p. 109°, $[\alpha]_D$ −1° (*c*, 1·96), were isomerised as described above for the preparation of "β-dihydroergosteryl acetate." The "αβ-ergostenyl acetate," recrystallised from methanol, had m. p. 93·5—94·5°, $[\alpha]_D$ +8° (*c*, 5·5), +7° (*c*, 2·9), +6° (*c*, 1·16), unchanged on further recrystallisation. Alkaline hydrolysis and benzoylation of the product furnished, after repeated crystallisation from chloroform–methanol, almost pure "β"-ergostenyl benzoate, m. p. 153—154°.

"αβ-Ergostenyl Acetate."—27·7 Mg. of "α"-ergostenol and 28·0 mg. of "β"-ergostenol (for prep. see *J.*, 1948, 783) were dissolved in pyridine (3 ml.), and acetylated and worked up in the usual way. After one recrystallisation from methanol, "αβ-ergostenyl acetate" was obtained in almost quantitative yield. It had m. p. 93·5—94·5°, undepressed on admixture with the neutral hydrogenation product, m. p. 93·5—94·5°, from "β-dihydroergosteryl acetate."

Preparation of iso*Ergosterone.*—Carefully purified ergosterone (10 g.) was dissolved in chloroform (100 ml.) and treated with dry hydrogen chloride at 0° for 1 hour. The reaction mixture was poured into cold sodium hydrogen carbonate solution, the chloroform solution washed with water, and the chloroform removed *in vacuo*. Crystallisation from ethyl acetate–methanol afforded *iso*ergosterone, m. p. 105°, in 60% yield. The yield was much reduced if ergosterone contaminated with mesityl oxide (from the Oppenauer oxidation) was employed. In our hands the procedure of Wetter and Dimroth (*Ber.*, 1937, **70**, 1665; cf. Heilbron, Kennedy, Spring, and Swain, *J.*, 1938, 869) gave *iso*ergosterone from ergosterone in only 20% yield.

Hydrogenation of iso*Ergosterone.*—5·8 G. of *iso*ergosterone and 150 mg. of platinum oxide in ethyl acetate (120 ml.) were shaken under hydrogen until 500 ml. had been absorbed (10 minutes). After removal of the catalyst by filtration and of the solvent by evaporation *in vacuo*, the crystalline product was dissolved in light petroleum (b. p. 40—60°) and chromatographed over alumina (Birlec grade H). A typical chromatogram is illustrated in the figure.

Coproergost-22(23)-en-3-one.—*Ketone* (B) (see text), recrystallised from acetone–methanol, had m. p. 110·5°, $[\alpha]_D$ −2° (*c*, 2·16), −1° (*c*, 1·75), $[M]_D$ −4° (Found: C, 84·2; H, 11·3. $C_{28}H_{46}O$ requires C, 84·4; H, 11·6%). The ketone showed no absorption over the range 220—260 mμ. The 2 : 4-dinitrophenylhydrazone, prepared in the usual way, was yellow and, after chromatography and recrystallisation from chloroform–methanol, had m. p. 199°.

Coproergost-22(23)-en-3(α)-ol.—The above ketone (300 mg.) in *n*-propanol (30 ml.) was reduced, on the boiling water-bath, by the addition of sodium (3 g.). The steroidal product was taken up in 95% ethanol (50 ml.), treated with excess of digitonin in the same solvent, and worked up in the usual way (Schönheimer, *Z. physiol. Chem.*, 1933, **215**, 59). A small amount of insoluble digitonide was rejected and the coproergost-22(23)-en-3(α)-ol was recrystallised from ethyl acetate–methanol; m. p. 149—150°, $[\alpha]_D$ −4° (*c*, 2·13), −4° (*c*, 1·29; micro-tube), $[M]_D$ −16° (Found: C, 83·8; H, 11·9. $C_{28}H_{48}O$ requires C, 84·0; H, 12·0%).

Coproergost-22(23)-en-3(α)-yl acetate, recrystallised from ethyl acetate–methanol, had m. p. 114—115°, $[\alpha]_D$ +16° (*c*, 1·43), $[M]_D$ +71° (Found: C, 81·3; H, 11·1. $C_{30}H_{50}O_2$ requires C, 81·4; H, 11·3%).

Coproergost-22(23)-en-3(α)-yl benzoate, recrystallised from chloroform–methanol, had m. p. 146°, $[\alpha]_D$

+9° (*c*, 1·44; micro-tube), $[M]_D$ +45° (Found: C, 83·4; H, 10·1. $C_{35}H_{52}O_2$ requires C, 83·3; H, 10·3%).

Coproergost-22(23)-en-3(α)-yl Acetate 22 : 23-Dibromide.—Coproergost-22(23)-en-3(α)-yl acetate (40 mg.) was dissolved in 1 : 1 ether–acetic acid (3 ml.) and treated with a slight excess of bromine in the same solvents. The ether was removed by evaporation at room temperature *in vacuo*, and the dibromide isolated by the addition of methanol and recrystallised from chloroform–methanol; it had m. p. 190° without decomposition (Found: Br, 26·9. $C_{30}H_{50}O_2Br_2$ requires Br, 26·6%).

Hydrogenation of Coproergost-22(23)-en-3-one in Neutral Solution.—The ketone (40 mg.) in ethyl acetate (20 ml.) was hydrogenated for 3 hours in presence of 50 mg. of platinum oxide. After removal of the catalyst by filtration and of the solvent by evaporation *in vacuo*, the product was chromatographed over alumina to give traces of hydrocarbon (eluted first) and the bulk as a sterol fraction m. p. 125—135°, saturated to $C(NO_2)_4$. The sterol was treated with digitonin in the usual way (see above), a small quantity of insoluble digitonide removed, and the bulk worked up (Schönheimer, *loc. cit.*) to give, after crystallisation from methanol, coproergostan-3(α)-ol, m. p. 139°. This was converted into the acetate, recrystallised from methanol, m. p. 99°, $[\alpha]_D$ +39° (*c*, 1·02; micro-tube), undepressed in m. p. by admixture with authentic material, m. p. 99°, $[\alpha]_D$ +39° (Barton and Miller, this vol., p. 337).

Ergost-22(23)-en-3-one.—*Ketone* D (see text), recrystallised from acetone–methanol, had m. p. 165·5°, $[\alpha]_D$ +8° (*c*, 1·90; micro-tube), +6° (*c*, 1·55; micro-tube), $[M]_D$ +28° (Found: C, 84·5; H, 11·3. $C_{28}H_{46}O$ requires C, 84·4; H, 11·6%). The ketone showed no absorption over the range 220—260 mμ. The yellow 2 : 4-dinitrophenylhydrazone, prepared in usual way, had m. p. 208—209°, after chromatography over alumina and crystallisation from chloroform–methanol.

Ergost-22(23)-en-3(β)-ol.—200 Mg. of the above ketone in *n*-propanol (20 ml.) were reduced by the addition of sodium (2 g.) on the boiling water-bath. The steroidal product, in hot 95% ethanol, furnished an insoluble digitonide which was decomposed in the usual way (Schönheimer, *loc. cit.*) to give *ergost-22(23)-en-3(β)-ol*, recrystallised from chloroform–methanol, m. p. 152°, $[\alpha]_D$ −9° (*c*, 2·07; micro-tube), −10° (*c*, 1·97, micro-tube), $[M]_D$ −40° (Found: C, 82·3; H, 12·0. $C_{28}H_{48}O,\frac{1}{2}H_2O$ requires C, 82·2; H, 12·0%).

Ergost-22(23)-en-3(β)-yl acetate, recrystallised from ethyl acetate–methanol, had m. p. 155·5°, $[\alpha]_D$ −17° (*c*, 1·42; micro-tube), $[M]_D$ −75° (Found: C, 80·9; H, 11·0. $C_{30}H_{50}O_2$ requires C, 81·4; H, 11·3%).

Ergost-22(23)-en-3(β)-yl benzoate, recrystallised from chloroform–methanol, had m. p. 140°, $[\alpha]_D$ −8° (*c*, 2·27; micro-tube), $[M]_D$ −40° (Found: C, 82·7; H, 10·4. $C_{35}H_{52}O_2$ requires C, 83·3; H, 10·3%).

Ergost-22(23)-en-3(β)-yl Acetate 22 : 23-Dibromide.—Ergost-22(23)-en-3(β)-yl acetate (40 mg.) in 1 : 1 ether–acetic acid (3 ml.) was treated with a slight excess of bromine in the same solvents. The *dibromide* crystallised from the reaction mixture and was purified by recrystallisation from chloroform–methanol; decomp. *ca.* 226° (Found: Br, 26·1. $C_{30}H_{50}O_2Br_2$ requires Br, 26·6%).

Hydrogenation of Ergost-22(23)-en-3-one in Neutral Solution.—The ketone (*D*) (see above) (13 mg.) was hydrogenated in ethyl acetate (20 ml.) for 3 hours, 25 mg. of platinum oxide being used. After the mixture had been worked up in the usual way, acetylation and recrystallisation from chloroform–methanol gave ergostanyl acetate, m. p. 144°, undepressed in m. p. when admixed with authentic material, m. p. 144°.

Ergosta-4(5) : 22(23)-dien-3-one.—*Ketone* (F) (see text), recrystallised from acetone–methanol, had m. p. 127·5—128·5°, $[\alpha]_D$ +43° (*c*, 4·63), +44° (*c*, 3·10; micro-tube), $[M]_D$ +174° (Found: C, 84·6; H, 11·0. $C_{28}H_{44}O$ requires C, 84·8; H, 11·1%). The ketone showed a strong absorption band in the ultra-violet in ethanol solution, $\lambda_{max.}$ 242 mμ., ε 18,200, characteristic for an αβ-unsaturated ketone. The red 2 : 4-*dinitrophenylhydrazone*, prepared in the usual way and purified by chromatography and recrystallisation from chloroform–methanol, had m. p. 242—243° (Found: N, 9·7. $C_{34}H_{48}O_4N_4$ requires N, 9·7%). The 4-phenylsemicarbazone, prepared as described previously (*J.*, 1948, 783) and recrystallised from chloroform–methanol had m. p. 229° (decomp.).

Oxidation of Brassicasterol.—Brassicasterol (150 mg.), obtained by hydrolysis of the brassicasteryl acetate, m. p. 151—153°, kindly supplied by Dr. H. E. Stavely, was oxidised by the Oppenauer method. The product was chromatographed over alumina and gave the following fractions (each after one recrystallisation from methanol):

(i)	100 ml. of light petroleum (b. p. 40—60°)	Nothing.
(ii)	350 ml. of 4 : 1 light petroleum (b. p. 40—60°)–benzene...	Traces of gum (mesityl oxide).
(iii)	25 ml. of 1 : 1 light petroleum (b. p. 40—60°)–benzene...	Ketonic material, m. p. 129°.
(iv)	25 ml. of benzene	Gum.
(v)—(xiii)	200 ml. of benzene each	All ketonic fractions, m. p. 123°.
(xiv)	50 ml. of 1 : 1 ether–methanol	Little unchanged brassicasterol.

Fractions (v)—(xiii) were combined and recrystallised from acetone–methanol, to give brassicastadienone, m. p. 127°, $[\alpha]_D$ +49° (*c*, 1·88; micro-tube), undepressed in m. p. by admixture with ergosta-4(5) : 22(23)-dien-3-one prepared as above. Recrystallisation of fraction (iii) yield 2 mg. of a ketone, m. p. *ca.* 135°.

Hydrogenation of Ergosta-4(5) : 22(23)-dien-3-one in Neutral Solution.—1·28 G. of pure ketone (*F*) (see above) were shaken in ethyl acetate (30 ml.) with platinum oxide (100 mg.) in an atmosphere of hydrogen until 85 ml. had been absorbed (1 minute). The product was chromatographed over alumina and gave coproergost-22(23)-en-3-one, m. p. 108—109°, $[\alpha]_D$ +1° (*c*, 1·48), undepressed in m. p. by admixture with ketone (*B*) above (m. p. 110°), and ergost-22(23)-en-3-one, m. p. 164—165°, $[\alpha]_D$ +8° (*c*, 0·50; micro-tube), undepressed in m. p. on admixture with ketone (*D*) above (m. p. 165°).

Ergost-22(23)-ene 22 : 23-Dibromide.—The hydrocarbon mixture (*A*) (see text) in 1 : 1 ether–acetic acid (5 ml.) was treated with a slight excess of bromine in the same solvents. The *dibromide* crystallised from the reaction mixture and after two recrystallisations from chloroform–acetone attained a reproducible decomposition point of 218° (Found: Br, 29·3. $C_{28}H_{46}Br_2$ requires Br, 29·4%).

Ergost-22(23)ene.—The above dibromide was treated in chloroform–acetic acid on the water-bath

for ½ hour with successive small portions of zinc dust. After filtration from excess zinc dust and working up of the product by recrystallisation from acetone, ergost-22(23)-ene, m. p. 107—108°, $[\alpha]_D$ −10° (*c*, 2·27; micro-tube), $[M]_D$ −38°, was obtained (Found: C, 87·1; H, 12·6. $C_{28}H_{48}$ requires C, 87·5; H, 12·5%).

Hydrogenation of Ergost-22(23)-ene in Neutral Solution.—25 Mg. of ergost-22(23)-ene were hydrogenated in ethyl acetate (30 ml.) for 3 hours, 100 mg. of platinum oxide being used. After removal of the catalyst by filtration and of the solvent by evaporation *in vacuo*, the product was recrystallised from chloroform–methanol to give ergostane, m. p. 82—83°, $[\alpha]_D$ +15° (*c*, 0·76; micro-tube), $[M]_D$ +58°.

Action of Hydrogen Chloride on Stigmasteryl Acetate.—After several hours' treatment of 300 mg. of stigmasteryl acetate, (m. p. 143°) in chloroform with excess of dry hydrogen chloride at 0° and working up of the product as described above for "β-dihydroergosteryl acetate," the starting material was (almost quantitatively) recovered, having m. p. 143°, not depressed by admixture with pure stigmasteryl acetate.

Hydrogenation of Ergost-14(15)-en-3(β)-ol.—Ergost-14(15)-en-3(β)-ol (0·3 g.) (*J.*, 1948, 783) was hydrogenated overnight in anhydrous ether (50 ml.) in presence of fresh platinum oxide. After being worked up in the usual way the product gave no colour in the Liebermann–Burchard reaction. One recrystallisation from methanol afforded ergostan-3(β)-ol, m. p. 141·5°, $[\alpha]_D$ +15° (*c*, 1·82), in almost quantitative yield. Use of 1 : 1 ether–acetic acid as solvent gave essentially the same result.

Ergostan-3-one.—This compound was prepared by chromic acid oxidation of ergostanol in the usual way and purified by chromatography over alumina. Recrystallised from ethyl acetate–methanol, it had m. p. 160°, $[\alpha]_D$ +33° (*c*, 1·45; micro-tube), $[M]_D$ +132°.

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381. *Some Catalysed Gas-phase Reactions of Aromatic Hydrocarbons. Part V. Interconversion of Alkylbenzenes. Disproportionation and Cracking Reactions.*

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Previous work (Parts I—IV, *J.*, 1947, 928; 1948, 73, 1700, 2154) is extended by a study of the reactions of ethyl- and *n*-propyl-benzene with dimethyl ether, and of the same hydrocarbons and toluene and *p*-xylene when passed slowly (liquid hourly space velocities of 0·06—0·10 hour^{-1}) in the absence of the ether over a silica–alumina catalyst at 450°. Scission of alkyl groups is the main reaction of ethyl- and propyl-benzene, whether or not the ether is present, and disproportionation is very slight, whereas the principal reactions of methylbenzenes are methylation in the presence of dimethyl ether, and disproportionation in its absence; isomerisation of *p*-xylene occurs concurrently in either case. The silica–alumina catalyst is shown to be particularly active in the synthesis of ethylbenzene from benzene and ethylene. The yields of the products of the various reactions are compared with those thermodynamically possible.

WE have shown previously (Given and Hammick, Part IV, *J.*, 1948, 2154) that, when a single xylene isomer is passed with dimethyl ether over a silica–alumina catalyst at 450°, about 22% is converted into trimethylbenzenes; isomerisation of the xylene occurs at the same time. We now find that, under the same conditions, only small yields of methylethyl- and methylpropyl-benzene are obtained from ethyl- and *n*-propyl-benzene respectively; the principal reaction in both cases is cracking, the main products containing fewer carbon atoms than did the original hydrocarbons. Thus there is a distinction between the behaviour of methyl- and other alkyl-benzenes; and it is clear that under the conditions used the methylation of alkylbenzenes, whatever the nature of the alkyl groups, is accompanied by various side-reactions (*e.g.*, isomerisation and cracking). We have therefore studied the reactions of a series of representative hydrocarbons (toluene, *p*-xylene, a xylene mixture, and ethyl- and *n*-propylbenzene) on passage over a silica–alumina catalyst in the absence of any alkylating agent, in order to gain further information concerning these side-reactions and to elaborate the distinction in behaviour between the various classes of hydrocarbons in their catalytic reactions. We have also determined the yield of ethylbenzene formed from benzene and ethylene at the same temperature and over the same catalyst.

As far as we are aware, the methylation of ethyl- and propyl-benzene by a gas-phase method has not previously been reported; the ethylation of benzene is, of course, well known (see,

e.g., O'Kelly, Kellett, and Plucker, *Ind. Eng. Chem.*, 1947, **39**, 154, who give full references to earlier work; also Hammick and Roberts, *J.*, 1948, 73). The reactions of pure hydrocarbons (*i.e.*, in the absence of an alkylating agent) over silica–alumina catalysts have attracted attention recently, since the collection of data relating to single compounds is important as a background to the industrial cracking and chemical refining of petroleum. Natanson and Kagan (*J. Phys. Chem. U.S.S.R.*, 1943, **17**, 381) passed toluene over a silica–alumina catalyst at a temperature (430°) and space rate of flow (0·05 hour^{-1}) comparable with those we have used, and found 25% of disproportionation to benzene and xylenes. Hansford, Myers, and Sachanen (*Ind. Eng. Chem.*, 1945, **37**, 671) report a similar disproportionation of *m*-xylene on the same type of catalyst at 538° and a liquid hourly space velocity (L.H.S.V.) of 1·05 hour^{-1}. On the other hand, Greensfelder, Voge, and Good (*Ind. Eng. Chem.*, 1945, **37**, 1168) state that *p*-xylene at 550° and L.H.S.V. 0·5 hour^{-1} suffers considerable cracking as well as disproportionation and report further that the composition of the recovered xylene approximates to that of the equilibrium mixture (calculated by Pitzer and Scott, *J. Amer. Chem. Soc.*, 1943, **65**, 803). These authors also record that for ethyl- and *n*-propyl-benzene under similar conditions (L.H.S.V., 1·7—1·9) removal of the alkyl groups, without disproportionation, is the main reaction. Thomas, Hoekstra, and Pinkston (*J. Amer. Chem. Soc.*, 1944, **66**, 1694) reached the same conclusions for ethylbenzene at 500° and L.H.S.V. 1·7—1·9 hour^{-1}.

Of this work, all but that of Natanson and Kagan was performed at temperatures and space rates of flow higher than those we used in our studies of reactions with dimethyl ether. In extending our work to the reactions of the hydrocarbons in the absence of ether, we have therefore restricted ourselves to the temperature (450°) and space rates of flow (L.H.S.V., 0·05—0·10 hour^{-1}) which we used in its presence.

We have compared the experimental yields of many of the reactions investigated with those theoretically possible, as calculated from equilibrium data. The extension of available information in the direction of lower rates of flow is of interest in this connection.

Experimental.

Materials.—The preparations of pure benzene, toluene, and *p*-xylene have already been described (Given and Hammick, *loc. cit.*). The xylene mixture was prepared by the methylation of benzene with dimethyl ether; its composition (*J.*, 1948, 2154) was ethylbenzene 0·4, *p*- 24·2, *m*- 54·3, and *o*-xylene 21·1%. The 1 : 4 alumina–silica catalyst, prepared by Messrs. Peter Spence Ltd., was that used in the earlier work.

The ethylbenzene was prepared by Clemmensen reduction of acetophenone. The product was heated under reflux with sodium to remove unsaturated compounds, and distilled; b. p. 136°, $n_D^{20°}$ 1·4959.

Table I.

Run no.	1	2	3	4	5	6	7	8
Hydrocarbon	toluene	*p*-xylene	xylene mixture	ethylbenzene	ethylbenzene	benzene	*n*-propylbenzene	*n*-propylbenzene
Alkylating agent	none	none	none	Me_2O	none	C_2H_4	Me_2O	none
Rate of flow, hydrocarbon, g./hr.	25·3	58	35·3	30	38·5	27·7	42	41
Space rate of flow, vol. liquid/vol. catalyst space/hr.	0·061	0·141	0·086	0·073	0·093	0·067	0·010	0·010
Rate of flow of alkylating agent, g./hr.	—	—	—	13·3	—	21·2	20·2	—
Molar ratio, hydrocarbon/other reactant	—	—	—	0·98	—	0·47	0·80	—
Yield, moles %. C_6	9·8	—	—	12·7	36·4	73·4	29·2	53·3
C_7	77·7	11·8	25·7	11·1	3·1 [a]	1·7 [a]	12·8	5·6
C_8	8·1	73·4 [b]	52·9	39·7	38·6	22·0	6·9	3·2 [a]
C_9	nil	11·7 [c]	16·9 [c]	8·9 [d]	2·4 [a]	nil	23·5	6·2
C_{10}	—	—	—	3·0 [a]	3·6 [a]	1·9 [a]	nil	nil
Total moles, liquid product	99·0	96·9	95·5	75·4	84·1	99·0	72·4	72·4

[a] These figures are less reliable than the others in the table, as the volumes of the cuts were small; they may be in error by 15% of the values quoted, whereas the rest are reliable to ±3—5%.

[b] The composition is given in Table III. We are indebted to Dr. Powell of Anglo-Iranian Oil Co. Ltd. for the analysis, which was made by the ultra-violet-spectroscopical method (Gordon and Powell, *J. Inst. Petrol.*, 1945, **31**, 428).

[c] These fractions distilled in the trimethylbenzene range, and the distillation curves, together with the refractive indices of successive portions of the distillates, indicated that ψ-cumene was the main component with small amounts (20% or less of each) of mesitylene and hemimellitene.

[d] Distilled entirely in the ethyltoluene range.

n-Propylbenzene was prepared by Clemmensen reduction of propiophenone; the partly unsaturated product was hydrogenated over Raney nickel; the material was fractionated in the Podbialniak still; b. p. 159°, $n_D^{20°}$ 1·4919.

The ethylene and nitrogen were cylinder gases used as supplied by the British Oxygen Company.

The apparatus, the Podbialniak still used in the analysis of the products, and the experimental methods, have been described previously (Part I, *J.*, 1947, 925; Part IV, *J.*, 1948, 2154). A slow stream of nitrogen (1—3 l. hour^{-1}) was used as a carrier gas in the experiments in which the reactions of a hydrocarbon in the absence of an alkylating agent were investigated.

Results.—All the reactions were performed at 450° over the silica–alumina catalyst. The rates of flow of the reactants and the yields of products are given in Table I. The contact times, calculated from the free space in the catalyst chamber (*i.e.*, volume of voids) and the volume of hydrocarbon vapour (at 450°/1 atm.) passed per hour, averaged about 45 seconds.

The yields are expressed as moles of product per 100 moles of aromatic hydrocarbon passed.

In runs 7 and 8 (*n*-propylbenzene) small cuts boiling near 60° were found; their refractive indices (material incompletely separated from benzene had $n_D^{20°}$ 1·4501) showed that they contained aliphatic hydrocarbons, presumably hexenes formed by polymerisation of propene. The yields calculated on the assumption that 2 moles of propylbenzene gave 1 mole of hexene, were 2·7% and 3·3%, respectively. The gaseous products of run 5 (ethylbenzene) contained an alkene of more than two carbon atoms (see analysis in Table II below), and the liquid products of the run also contained a little low-boiling material; thus some butenes may have been formed.

There was no evidence of the presence of any C_{12} hydrocarbons in the products of the propylbenzene experiments.

Analyses of 60—100-c.c. samples of the gaseous products of the reactions are given in Table II. The samples were collected at approximately the middle of the reaction periods.

TABLE II.

Run.	Aromatic hydrocarbon passed.	Alkylating agent.	Percentage by volume of gaseous products. Me_2O.	C_mH_{2m}.	CO_2.	CO.	H_2.	C_nH_{2n+2}.	*n*.
4	Ethylbenzene	Me_2O	0·1	9·0	0·9	8·5	4·2	77·4	1·2
5	Ethylbenzene	none	nil	37·5	nil	1·2	30·8	30·6	2·35
7	*n*-Propylbenzene	Me_2O	0·5	20·7	1·2	5·2	8·9	63·6	1·5
8	*n*-Propylbenzene	none	nil	14·6	nil	1·3	26·2	57·8	3·1

CONCLUSIONS.

Disproportionation of Methylbenzenes.—The results of experiments 1—3 (Table I) show that disproportionation has occurred, but very little cracking; the disproportionated products are formed in nearly equivalent amount, and the total of these products and unchanged starting material is 95—99% in each case. Our yields resemble those of Hansford, Myers, and Sachanen (*loc. cit.*), and Greensfelder, Voge, and Good (*loc. cit.*), which is perhaps surprising in view of the wide difference between their working temperature and rates of flow, and ours (see Introduction). However, we do not find the extensive cracking of *p*-xylene reported by the latter authors.

In spite of the low L.H.S.V. we have used, the disproportionation of neither toluene nor the xylenes proceeds to equilibrium in a single pass. The equilibrium constants of the reactions in the vapour state at 450° (Pitzer and Scott, and Taylor *et al.*, *locc. cit.*) are:

$$2\text{PhMe} \rightleftharpoons \underset{\text{(equilibrium mixture)}}{C_6H_6 + C_6H_4Me_2} \qquad K_p = 0{\cdot}29 \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$\underset{\text{(equilibrium mixture)}}{2C_6H_4Me_2} \rightleftharpoons \text{PhMe} + \underset{\text{(equilibrium mixture)}}{C_6H_3Me_3} \qquad K_p = 1{\cdot}07 \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

At equilibrium the products of reaction (1) should, therefore, consist of 47% toluene and 26·5% each of benzene and xylenes, whilst those of reaction (2) should contain 44·4% of C_8 aromatics, and 27·8% each of toluene and trimethylbenzenes. It appears that in our experiments the disproportionation of the xylene mixture approaches the equilibrium state, but the corresponding reactions of toluene and *p*-xylene have stopped some way short of equilibrium. (The actual composition of the C_8 and C_9 products were near enough to the equilibrium values for the comparisons to be fair; it should be noted that in the *p*-xylene experiment (run 2 in Table I) it is a C_8-mixture and not *p*-xylene which is involved in the equilibrium with toluene and trimethylbenzenes, since the single isomer rearranges in the course of the reaction.)

Isomerisation of Xylene.—The xylene recovered from run 2, in which *p*-xylene was passed over the catalyst, contained only 35·7% of the *para*-isomer, so that isomerisation occurs as well as disproportionation. The composition of this recovered xylene (Table III) is very nearly the same as that of the xylene recovered from our methylation of the *para*-isomer with dimethyl ether (see Part IV, *loc. cit.*, Table II, p. 2154), and both analyses are close to the equilibrium composition

(Taylor, Wagman, Williams, Pitzer, and Rossini, *J. Res. Nat. Bur. Stds.*, 1946, **37**, 95). The two analyses are reported in Table III, together with the equilibrium concentrations, and the analysis of Greensfelder *et al.* (*loc. cit.*), who have also observed the catalytic isomerisation of *p*-xylene.

TABLE III.

	Temp., °C.	Ethyl-benzene.	Xylene.		
			para-.	*meta*-.	*ortho*-.
Isomerisation of *p*-xylene (run 2, this paper)	450	0·0%	35·7%	45·5%	18·8%
Methylation of *p*-xylene (Part IV)	450	0·4	33·8	46·1	19·3
Equilibrium (Taylor *et al.*)	450	9·0	21·2	47·3	22·5
,, ,, ...	550	11·0	23·0	45·5	20·5
,, (Pitzer and Scott)	450	—	21	59	19
,, ,, ...	550	—	21	58	21
Isomerisation of *p*-xylene (Greensfelder *et al.*)	550	—	27·4	47·3	25·3

We showed in Part IV (*loc. cit.*) that, when the other xylene isomers are passed with dimethyl ether over the catalyst, the composition of the xylene isolated from the products approximated to that of the equilibrium mixture. Considered with the figures quoted above, this shows that the isomerisation occurs independently of an alkylation reaction which may be proceeding simultaneously; *i.e.*, the presence of dimethyl ether is not an essential factor for isomerisation.

Reactions of Ethyl- and Propyl-benzenes.—From the analyses of the products of runs 5 and 8 (see Table I) it is seen that, when either ethyl- or propyl-benzene is passed alone over the silica–alumina catalyst, the principal reaction is scission of the whole side-chain, although some cracking in the middle of the chain evidently also occurs; it will be noted that the diethyl- and dipropyl-benzene formed in runs 5 and 8 respectively are far less than equivalent to the benzene produced, which confirms the conclusion that the reaction is indeed cracking and not disproportionation. The analyses of the gaseous products support the same conclusion (see below). The results quoted here are qualitatively similar to those of the experiments, already referred to in the introduction, of Greensfelder, Voge, and Good (*loc. cit.*) and Thomas, Hoekstra, and Pinkston (*loc. cit.*), although we find more extensive cracking at 450° than they did at 500—550°, presumably because of the much lower L.H.S.W. we have used.

The rapid cracking of C_2 and C_3 side-chains is clearly an important factor in determining the products of the reactions of ethyl- and *n*-propyl-benzene with dimethyl ether; in runs 4 and 7 (Table I), the yields of monomethylated products from ethyl- and propyl-benzene were 8·9% and nil, respectively, whilst substantial amounts of benzene and toluene were formed (together with some C_8 hydrocarbons from the propylbenzene). In contradistinction to this situation, we have found (Part IV, *loc. cit.*) that more than 20% of the monomethylated derivative, but very small amounts of demethylated products, are formed in the reaction of toluene or a xylene with dimethyl ether under the same conditions. Thus in the reactions of methylbenzenes, removal of methyl groups by cracking is much slower than methylation by dimethyl ether, or disproportionation in its absence; isomerisation of xylenes occurs freely whether the ether is present or not. On the other hand, the cracking of the side-chains of ethyl- and *n*-propyl-benzenes is much faster than the methylation, disproportionation, or isomerisation of the same compounds (the two last-named were found to occur to only a slight extent, if at all). Clearly the relative velocities of the various reactions depend markedly on the size of the alkyl side-chain attached to the benzene nucleus.

Gaseous Products of the Reactions of Ethyl- and n-*Propylbenzene.*—The principal gaseous products of the reactions of these two hydrocarbons, in the absence of dimethyl ether, are hydrogen, alkene, and alkane (see Table II); the alkane contains approximately the same number of carbon atoms as the side-chain of the hydrocarbon from which it was derived. In addition, there was some evidence (see Experimental section) of dimerization of the ethylene and propene to butenes and hexenes. One would expect the formation of some of the corresponding alkene in the cracking of an alkylbenzene, *e.g.*, $PhEt = C_6H_6 + C_2H_4$, and some dimerization might well occur; but one would not expect either hydrogen or an alkane to be formed. Greensfelder *et al.* (*loc. cit.*) found propane and propene, but no hydrogen, in the gaseous products of the cracking of *n*-propylbenzene. Thomas (*J. Amer. Chem. Soc.*, 1944, **66**, 1586) has reported an apparent gain in hydrogen during cracking of octenes on a silica–alumina catalyst at 375° and accounted for it by establishing that part of his products were hydrogenated with the simultaneous formation of a carbonaceous deposit poor in hydrogen; a carbonaceous deposit was also formed in our experiments, so that the " gain " of hydrogen we observe may be due to a disproportionation of similar type. The gases formed in the reactions of the alkyl-

benzenes with dimethyl ether have the compositions one would expect of a mixture of the decomposition products of the ether (see Given and Hammick, Part I, *loc. cit.*) with those of the hydrocarbons.

Reaction of Benzene and Ethylene.—The conversion of benzene and ethylene into ethylbenzene was 22% per pass (see run 6, Table I). This is much higher than the yield achieved by Hammick and Roberts (Part III, *J.*, 1948, 73), whose maximum conversion was 6·8%, using a bauxitic clay at a similar temperature and rate of flow. O'Kelly, Kellett, and Plucker (*loc. cit.*) obtained only 6—14% of ethylbenzene when they passed benzene and ethylene over a silica–alumina catalyst at 450—500° and 50—75 lb. per sq. in., but they used a space velocity some thirty times ours. Our catalyst would appear to be particularly active for this reaction.

Equilibrium between Benzene, Ethylene, and Ethylbenzene.—Since we have performed this reaction in both directions, we were interested to compare the experimental results with the calculated equilibrium compositions.

The equilibrium constant of the vapour-phase reaction, $C_6H_6 + C_2H_4 \rightleftharpoons PhEt$, is $K_p = 8{\cdot}61$ at 450° (Taylor *et al.*, *loc. cit.*), so that, if we start with benzene and ethylene in the ratio used in experiment 6 (Table I), the equilibrium mixture should contain 7·4% of benzene, 56·5% of ethylene, and 36·1% of ethylbenzene. We were not able to determine the total ethylene in the products, but from the above figures we see that at equilibrium the liquid products should consist of 17% of benzene and 83% of ethylbenzene, whereas our product contained 77% of benzene and 23% of ethylbenzene, so that our relatively high conversion is still some way short of that theoretically possible. If an equal number of molecules of benzene and ethylene is present in the equilibrium mixture (*i.e.*, when synthesis is performed with a 1 : 1 mixture, or when ethylbenzene is cracked), the mixture should contain 24·4% each of benzene and ethylene, and 51·2% of ethylbenzene, and the liquid products should consist of 32·3% of benzene and 67·7% of ethylbenzene. The mixture of the two liquids given by the experimental cracking of ethylbenzene contained 46·5% of benzene, and 53·6% of ethylbenzene, apparently beyond equilibrium; but the agreement is probably satisfactory, in view of the occurrence of side-reactions. A similar comparison of the cracking of propylbenzene with the corresponding theoretical equilibrium leads to the same conclusion.

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382. *The Structure of Potassium Dinitrososulphite.*

By E. G. COX, G. A. JEFFREY, and H. P. STADLER.

The crystal structure of potassium dinitrososulphite has been determined by *X*-ray analysis in order to discover the configuration of the anion. Without any structural assumptions this configuration has been shown to be $O_3S{\cdot}N(O){:}NO$; the sulphur atom is surrounded tetrahedrally by three oxygen atoms at 1·43 A. distance and one nitrogen at 1·63 A; the two nitrogens and the three atoms attached to them are all coplanar, and the N–N distance of 1·30 A. corresponds to a double bond. The two N–O distances are 1·35 A. The anions are situated on mirror planes of the space-group *Pnma*, with the K atoms in general positions approximately half-way between these planes. The conflicting chemical evidence reported in the literature is discussed in relation to these results.

The interesting observation has been made that partial replacement of potassium by sodium causes a reorientation of the anions so that the space-group becomes *Pcmn*.

ALTHOUGH potassium dinitrososulphite was first prepared nearly 150 years ago and has been the subject of many investigations since, its chemical properties appear to show such contradictions that none of the configurational formulæ proposed has been able to command general acceptance. As already briefly reported (Cox, Jeffrey, and Stadler, *Nature*, 1948, **162**, 770), we have now been able to determine its structure by *X*-ray methods, without using chemical evidence which might be open to more than one interpretation. The result enables us to account for many of the properties of the dinitrososulphite ion, but also shows the need for further study of some of its reactions.

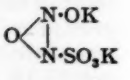
In 1801 Davy (*Bibl. Brit.*, Série Sci. Arts, 1802, **20**, 358) passed nitric oxide into an alkaline solution of potassium sulphite to produce a white crystalline precipitate which evolved nitrous oxide on heating. He called the compound " nitroxide of potash," but did not purify and analyse it. Pelouze (*Ann. Chim. Phys.*, 1835, **60**, 151; *Annalen*, 1835, **15**, 240) synthesized the

compound from two volumes of nitric oxide and one volume of sulphur dioxide with excess of alkali, and established the composition as $K_2SO_5N_2$ by direct analysis; he also showed that the excess of alkali stabilized the salt but was not essential for the preparation. Some fifty years later the interest in the constitution of chamber crystals and related compounds stimulated a series of further investigations. Divers and Haga (*J.*, 1885, **47**, 203) found that reduction of the salt with sodium amalgam gave sulphite and hyponitrite, and, regarding this reaction as analogous to the formation of sulphite and sulphide from thiosulphate, they formulated it as

$$(SO_3K)\cdot(N_2O_2)\cdot K + 2Na = Na(N_2O_2)K + (SO_3K)Na$$

They called the salt a (hypo-)nitrososulphate, but did not at this stage assign a structure to the N_2O_2 group or discuss its linkage to the sulphur atom.

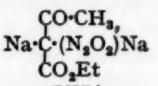
The formula (I), which, as will be seen, is essentially correct, was proposed a few years later by Raschig (*Annalen*, 1887, **241**, 232) for a different substance which he had prepared and which he thought was an isomer of Divers and Haga's salt. Raschig adopted the structure (I) because his substance gave hydrated potassium hydroxylaminedisulphonate (II) and nitrous oxide when he attempted to recrystallise it from dilute potassium hydroxide, but when Divers and Haga (*J.*, 1895, **67**, 452) showed that the supposed isomer was really a mixed salt of potassium nitrite and hydrated basic hydroxylaminedisulphonate (III) he (" Schwefel- und Stickstoffstudien," 1924, p. 108) withdrew the formula (I) and supported that of Hantzsch (*Ber.*, 1894, **27**, 3264) (IV) for the nitrososulphite.

(I.) $O\cdot N\cdot N\langle {O-K \atop SO_3K}$ (II.) $HO\cdot N(SO_3K)_2,2H_2O$ (III.) $(KSO_3)_2N\cdot OH,(KSO_3)_2N\cdot OK,H_2O$ (IV.) 

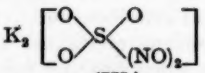
(V.) $NH_2\cdot SO_3Na$

(VI.) $H_2N\cdot NH\cdot SO_3Na$

(VIII.) $KO\cdot N{:}N\cdot O\cdot SO_3K$



(VII.)



(IX.)

Like Raschig's original formula, Hantzsch's *iso*nitroamine configuration includes an N–S link for which evidence was forthcoming from the reduction to amino- and hydrazino-sulphonates (V) and (VI) (Divers and Haga, *J.*, 1896, **69**, 1610; Raschig, *op. cit.*), but the principal argument in its favour was an analogy with Traube's (*Ber.*, 1894, **27**, 1507) ethyl acetoacetic *iso*nitroamine (VII). Divers and Haga, on the other hand, emphasized the formation of sulphate, both in the reduction with sodium amalgam and quantitatively by decomposition in the presence of acids. They were particularly impressed by the rapidity of the precipitation of barium sulphate on acidification of a solution of the dinitrososulphite and barium chloride; they argued that the sulphate group must be preformed in the original compound, and gave the formula (VIII).

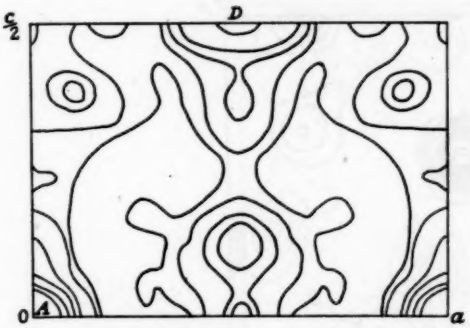
Finally, in 1933, Weitz and Achterberg (*Ber.*, **66**, 1718) showed that $K_2SO_5N_2$ reacted with freshly precipitated ferrous sulphide to form Roussin's black salt, $K[Fe_4(NO)_7S_3]$, and concluded that the nitrososulphite contained a pair of NO groups co-ordinated to the sulphur atom as in (IX). They apparently arrived at no result, however, which in any way enabled them to elaborate upon this formula, which is, in effect, merely a restatement of Divers and Haga's first suggestion of 1885.

There appeared therefore to be little possibility of assigning an entirely satisfactory formula to potassium dinitrososulphite on chemical evidence alone, and the problem seemed appropriate for investigation by *X*-ray structure analysis. The probability of a successful solution of the problem in this way, without recourse to conflicting chemical evidence, was greatly increased when later it was discovered that the ammonium and thallium salts were isomorphous with the potassium salt, and would therefore enable the structure analysis to be made without any preliminary assumptions about the configuration of the molecules.

Preliminary X-Ray Investigation.—Potassium dinitrososulphite crystallises in orthorhombic needles with a unit cell of dimensions $a = 7{\cdot}076 \pm 0{\cdot}003$ *kX*, $b = 8{\cdot}13 \pm 0{\cdot}05$ *kX*, $c = 9{\cdot}930 \pm 0{\cdot}007$ *kX*, containing four molecules of $K_2SO_5N_2$. With the first crystals, on which the bulk of the intensity measurements were made, the observed extinctions were $\{0kl\}$ absent for $k + l$ odd, and $\{hk0\}$ absent for h odd, so that the space-group is either *Pna* or *Pnma*. From some crystals, however, there was a moderately strong (110) reflexion which is not in agreement with either of these space-groups. A complete explanation of this was discovered later (see below), but because of the uncertainty it introduced and in view of the nature of the problem, it was decided to proceed as far as possible with the structure analysis without definite commitment as to the space-group.

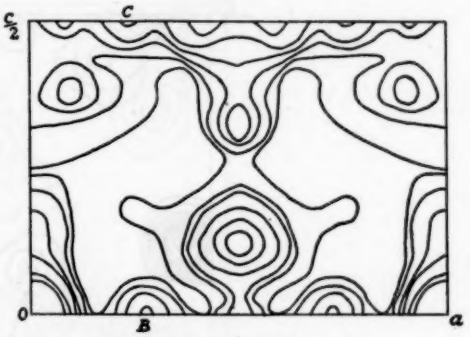
A decision between the possible orthorhombic space-groups is not required for the calculation of the Patterson F^2 syntheses, and so when the necessary intensities had been measured the projections in the three principal zones were computed. Their contour maps showed that the vector peaks were mainly distributed in the layers $y = 0, \pm \frac{1}{4}$, and $\frac{1}{2}$, and suggested that the relatively heavy K and S atoms lie in planes $\frac{1}{4}b$ apart. The F^2 sectional syntheses at $y = 0$, $\frac{1}{4}$, and $\frac{1}{2}$ were therefore evaluated, but owing to the similarity in scattering power of potassium and sulphur, and the uncertainty about the space-group, it was not possible at this stage to identify the various K–S, K–K, and S–S peaks. A similarity between the sections at $y = 0$ and $y = \frac{1}{2}$ (Figs. 1 and 2) confirmed the tendency to a halving of the b-axis, which had previously been inferred from the alternation of weak and strong layer lines in the [b] rotation photograph. When the isomorphous thallium salt was examined, this [b] halving was much more pronounced, providing strong evidence that it was the cationic lattice which was wholly or nearly halved.

FIG. 1.



Patterson section at y = 0.

FIG. 2.



Patterson section at y = ½.

On an F^2 ($h0l$) projection of the thallium salt, the Tl–Tl vectors were easily identified, and gave the (x, z)-co-ordinates of four of the cations, the other four being related by a shift of $\frac{1}{2}y$ on the evidence of the pseudo-halving. The translations of the heavy atoms correspond to $(\frac{1}{2} + x, \frac{1}{2} - z)$, $(\frac{1}{2} - x, \frac{1}{2} + z)$, *i.e.*, to the projection group *Pca* (Patterson, *Z. Krist.*, 1935, **90**, 543), which is in accordance with the space-groups *Pna* or *Pnma*.

Fourier Syntheses.—Using the phase relationships of this plane-group, the signs of the structure factors of the planes in the $\{h0l\}$ zone were calculated with the assumption that they were determined solely by the thallium contributions. A Fourier F($h0l$) projection was then obtained which showed several appreciable peaks in addition to those of the thallium atoms. One of these peaks was identified as originating from a sulphur atom, so it was then possible to make a partial interpretation of the F^2 synthesis of the potassium salt at $y = \frac{1}{4}$, *i.e.*, the level at which all the K–S vector peaks were expected to appear.

Any further attempts to interpret the thallium projection with the object of locating the lighter atoms was considered injudicious in view of the effect of absorption errors on the intensity measurements. But with the knowledge of both the potassium and sulphur (x, z)-parameters, many of the signs of the $\{h0l\}$ structure factors of the potassium salt could be ascertained. From these a Fourier F projection was calculated which confirmed the K and S positions and showed additional peaks due to oxygen or nitrogen atoms of the anion. When these were also allowed for, an F($h0l$) projection of fairly good resolution was obtained which is shown in Fig. 3*a*. In it the K and S positions (marked as such) are easily identified, and although there is a good deal of overlapping of the anions, the sulphur peak at S_1 appeared to be surrounded tetrahedrally by four light atoms, I placed at A_1, II and III at B_1, and IV overlapping another sulphur at S_2. The distance between the peaks was of the correct order of magnitude for S–O or S–N bonds, and agreed well with the assumption of a tetrahedral arrangement of atoms round the sulphur. From the height of the peaks it seemed likely that another atom could be accommodated at A_1, and of the remaining two light atoms one could be placed at C. There was no possibility at that stage of distinguishing between nitrogen and oxygen positions, so it was not known which of the seven light atoms in $K_2SO_5N_2$ had been located in the (x, z)-projection. In the absence of information about the y-co-ordinates it was not possible to postulate a likely configuration of the anion, whereby the position of the last atom could be determined. It had become necessary then to consider the y-parameters in the structure, and at the same time discuss further evidence

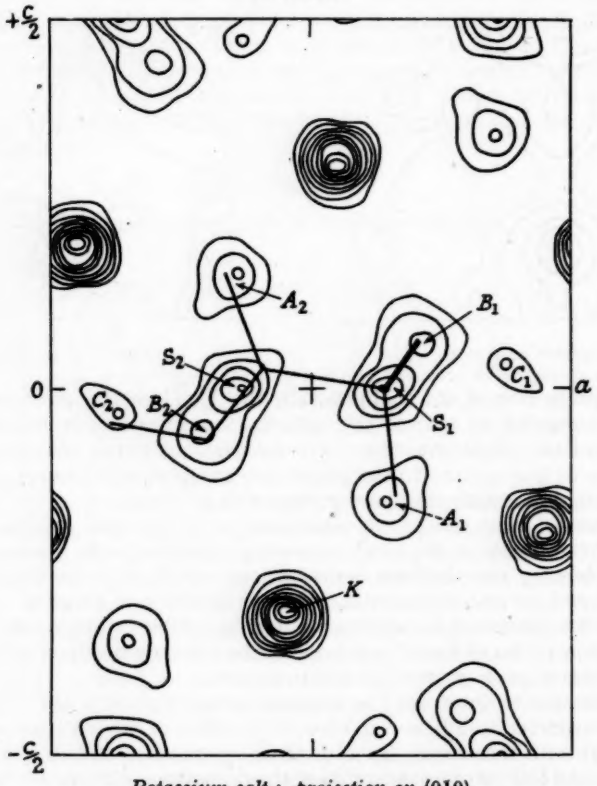
relating to the space-group. Making an arbitrary choice of origin, the y-levels of the cations were taken as 0 and $\frac{1}{2}$. The sulphur atoms were then expected to lie at $y = \frac{1}{4}$ and $\frac{3}{4}$, in accordance with the Patterson projections and the identification of K–S peaks in the section at $y = \frac{1}{4}$. This was fully confirmed by the following interpretation of the F^2 sectional syntheses.

From the F(hol) projection, the sulphur co-ordinates in one-sixtieths of the cell edges are (21, y_1, 0), (39, y_2, 0), (9, y_3, 30), (51, y_4, 30). Taking $y_1 = 15$, these give rise to S–S vectors as shown in Table I.

TABLE I.

	21, 15, 0	39, y_2, 0	9, y_3, 30	51, y_4, 30
21, 15, 0	0, 0, 0 *A*	18, y_2-15, 0 *B*	12, y_3-15, 30 *C*	30, y_4, 30 *D*

FIG. 3*a*.



Potassium salt : projection on (010).

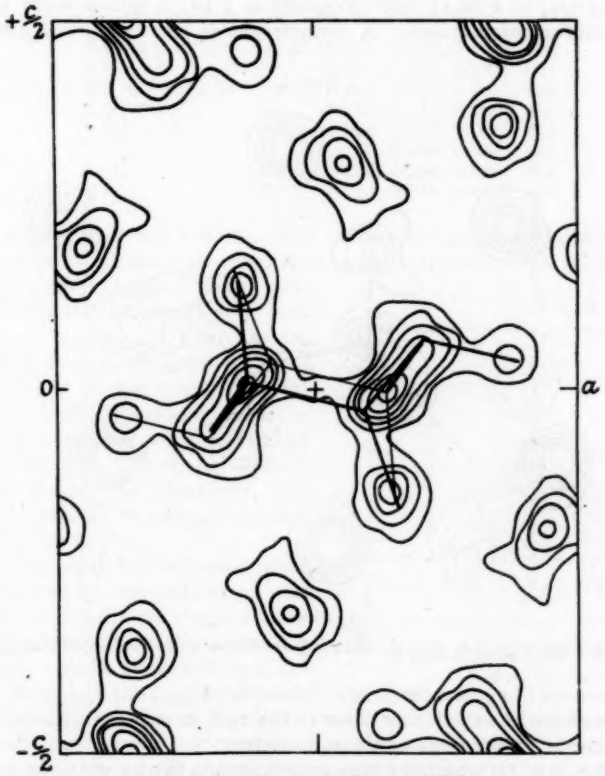
(*Note : The contours in Figs.* 3—5 *are on an arbitrary scale, and the contour interval on* S *and* K *peaks double that elsewhere.*)

The peaks B and C were found on the F^2 section at $y = \frac{1}{2}$ (Fig. 2), and D appeared at $y = 0$ (Fig. 1), whence it follows that $y_2 = y_3 = \frac{3}{4}$, and $y_1 = y_4 = \frac{1}{4}$. This gives four positions to the sulphur atoms which are of the form $(x, \frac{1}{4}, z)$, $(\bar{x}, \frac{3}{4}, \bar{z})$, $(\frac{1}{2} - x, \frac{3}{4}, \frac{1}{2} + z)$ and $(\frac{1}{2} - x, \frac{1}{4}, \frac{1}{2} - z)$, and correspond to the four-fold positions of the space-group *Pnma*. It appears, therefore, that both the potassium and the sulphur atoms have parameters which conform to *Pnma*, and, for the sole purpose of calculating the phases of $\{hk0\}$ and $\{0kl\}$, the structure was assumed to have the symmetry of this space-group. This meant that the anion was assumed to have a mirror plane of symmetry; it also meant that the (110) reflexion was being ignored at this stage in the analysis. The Fourier projections from the structure factors in the $\{hk0\}$ and $\{0kl\}$ zones confirmed the tetrahedral arrangement of light atoms around the sulphur but, apart from showing a concentration of unresolved peaks at $y = \pm\frac{1}{4}$, did not materially add to the information about the structure. In particular, they gave no clue as to the whereabouts of the missing

atom, and it became apparent that the solution of the configurational problem had to be sought by interpreting the (*h*0*l*) projection.

Although the ammonium salt had been reported by Pelouze as $(NH_4)_2SO_5N_2,H_2O$ it was found on *X*-ray examination to be isomorphous with the potassium and the thallium salt, so this salt too must be anhydrous. This isomorphism provided a new approach to the problem of determining the (*h*0*l*) phases. Comparing the relative intensities of corresponding reflexions of the ammonium and potassium salts, if $|F_{K\ salt}| > |F_{NH_4\ salt}|$ then $F_{K\ salt}$ must have the same sign as the cation contribution, and if $|F_{K\ salt}| < |F_{NH_4\ salt}|$, then $F_{NH_4\ salt}$ must have the opposite sign to the cation contribution. Since the cation contribution could be calculated, the sign of the other member of the inequality could usually be inferred by equating $|F_{K\ salt}| - |F_{NH_4\ salt}|$ to the difference between the two cation components.

FIG. 3*b*.



Ammonium salt : projection on (010).

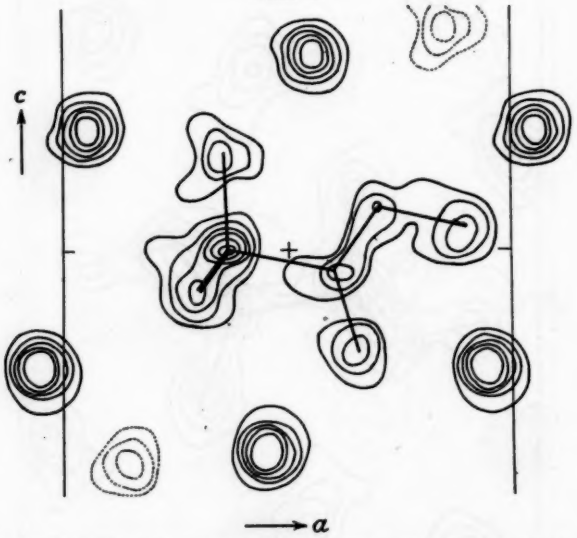
In this way it was possible to obtain an F(*h*0*l*) projection for the ammonium salt which was independent of the previously derived anion positions, and was more reliable because absorption errors are very much smaller for the ammonium than for the potassium salt. Thus it was hoped that the peak corresponding to the seventh light atom, thought to be obscured in the potassium salt projection, would be located; but the ammonium salt projection was found to confirm in every detail that of the potassium salt, and thus definitely showed that the seventh atom must be in a position overlapping other atoms in a region of high electron density on the projection.

A useful guide to the solution of the problem was found in the optical and morphological properties of the crystals, which are highly birefrigent with the highest refractive index along [100] and the lowest along [010]. This indicates [100] as the direction of the highest bond density and probably therefore that of elongation of the anion, a choice which is supported by a marked cleavage on (001). The low refractive index along [010] and the fact that this is the needle direction of the crystals pointed to a structure in layers parallel to (010).

A configuration which corresponds to these general observations and fits the projections was obtained by connecting an atom V at C_2 (Fig. 3*a*) to the sulphur at S_1 through a chain of two atoms VII and IV; the previously missing atom VII overlaps II and III of the other anion at B_2 and IV is superimposed on the sulphur at S_2, giving an ion in which all the atoms except II and III (projected at B_1) lie in a mirror plane parallel to (010). As a result the two anions overlap in the (*h*0*l*) projection as shown in Fig. 3*b*. The only possible chemical identification of the light atoms in this arrangement is $O_3S{-}N\begin{smallmatrix}N{-}O\\O\end{smallmatrix}$ (see also Fig. 7).

A detailed model was then constructed using the bond lengths found in the potassium sulphamate structure (Brown and Cox, *J.*, 1940, 1) for the bonds round the sulphur atom, *viz.*, S–O = 1·44, S–N = 1·57 A., which seemed compatible with the projection. The remaining interatomic distances were chosen by comparing the projection with models based on values given by Pauling (" Nature of the Chemical Bond "). The best agreement was obtained with N=N = 1·28 A., $N_{IV}{-}O_{VI}$ = 1·36 A., and $N_{VII}{=}O_V$ = 1·15 A., which were then used as basis for (*h*0*l*) structure factor calculations. A comparison of the calculated and measured values

FIG. 4.



Section projection from y = 0 *to* y = ½, *showing an anion with its complete cation environment.*

gave an average difference (" agreement index ") $\Delta = \Sigma(|F_{obs.}| \sim |F_{calc.}|)/\Sigma|F_{obs.}| = 0{\cdot}28$, and indicated that the model was sufficiently close to the real structure to justify proceeding with a three-dimensional Fourier refinement of the parameters.

Since all the evidence so far pointed to the existence of a mirror plane of symmetry in the ion, this assumption was made in calculating the phase angles of the general (*hkl*) structure factors. A section projection of a single anion was thus obtained from a synthesis evaluated between the limits $y = 0$ and $\frac{1}{2}$ (Fig. 4).

$$\int_{y=0}^{\frac{1}{2}} \rho(xyz)\,.\,dy = 4/A\,.\,[\Sigma\Sigma F(h0l)\,.\cos 2\pi hx/a\,.\cos 2\pi lz/c - \sum_{h+l\text{ even}}\Sigma F(h0l)\,.\sin 2\pi hx/a\,.\sin 2\pi lz/c] - \sum_{h+l\text{ odd}}$$

$$8/A\,.\,[\Sigma\Sigma\Sigma\frac{1}{\pi k}[F(hkl)\,.\sin 2\pi hx/a\,.\cos 2\pi lz/c + \sum_{h+l\text{ even},\ k\text{ even}}\Sigma\Sigma\frac{1}{\pi k}F(hkl)\,.\cos 2\pi hx/a\,.\sin 2\pi lz/c] \sum_{h+l\text{ odd},\ k\text{ odd}}$$

The changes in the atomic co-ordinates which resulted from this section projection were very small, and so it was followed by the calculation of the sectional syntheses at $y = \frac{1}{4}$, 0, and $\frac{1}{12}$, which are shown superimposed in Fig. 5. The y-parameters of O_{II} and K were obtained by line syntheses.

The co-ordinates from these syntheses are shown in Table II, and the bond lengths and angles in Table III. Fig. 6*a* gives a general view of the whole structure.

TABLE II.

Table of co-ordinates.

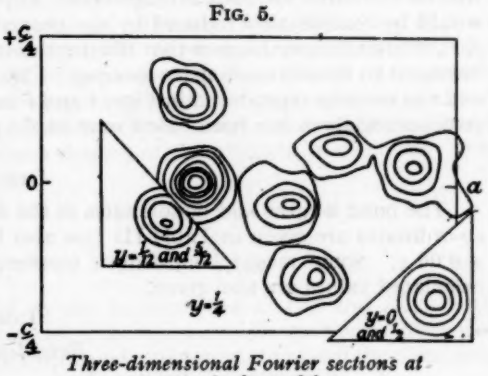
Atoms in positions (*c*) and (*d*) of space-group *Pnma* ("Int. Tables for the Determination of Crystal Structures," p. 138.)

$$(c)\ (x, \tfrac{1}{4}, z),\ (\bar{x}, \tfrac{3}{4}, z),\ (\tfrac{1}{2} - x, \tfrac{3}{4}, \tfrac{1}{2} + z),\ (\tfrac{1}{2} + x, \tfrac{1}{4}, \tfrac{1}{2} - z)$$
$$(d)\ \pm\,|\,(x, y, z),\ (\tfrac{1}{2} + x, \tfrac{1}{2} - y, \tfrac{1}{2} - z),\ (\bar{x}, \tfrac{1}{2} - y, \bar{z}),\ (\tfrac{1}{2} + x, y, \tfrac{1}{2} - z)\,|$$

8 K	in positions	(*d*)	at (0·055, 0·995, 0·190), etc.
8 O_{II} and O_{III}	at	(*d*)	,, (0·290, 0·110, 0·935), etc.
4 S	in positions	(*c*)	,, (0·365, 0·250, 0·005), etc.
4 O_I	,,	(*c*)	,, (0·350, 0·250, 0·150), etc.
4 N_{IV}	,,	(*c*)	,, (0·590, 0·250, 0·965), etc.
4 O_{VI}	,,	(*c*)	,, (0·650, 0·250, 0·835), etc.
4 O_V	,,	(*c*)	,, (0·895, 0·250, 0·030), etc.
4 N_{VII}	,,	(*c*)	,, (0·715, 0·250, 0·065), etc.

From these atomic parameters the structure factors of the principal zones were calculated for both the ammonium and the potassium salt, and compared with those measured experimentally. The agreement indices were calculated separately for different values of h, and showed no systematic tendency to decrease for increasing orders of h, such as would arise from any deviations from the mirror plane of symmetry. There is no doubt, therefore, that the atomic arrangement conforms very closely to the symmetry of *Pnma*, and that, as already inferred from the Patterson syntheses, the structure of $K_2SO_3N_2$ should be assigned to this space-group rather than to *Pna*.

FIG. 5.



Three-dimensional Fourier sections at $y = 0, \frac{1}{12}$, *and* $\frac{1}{4}$.

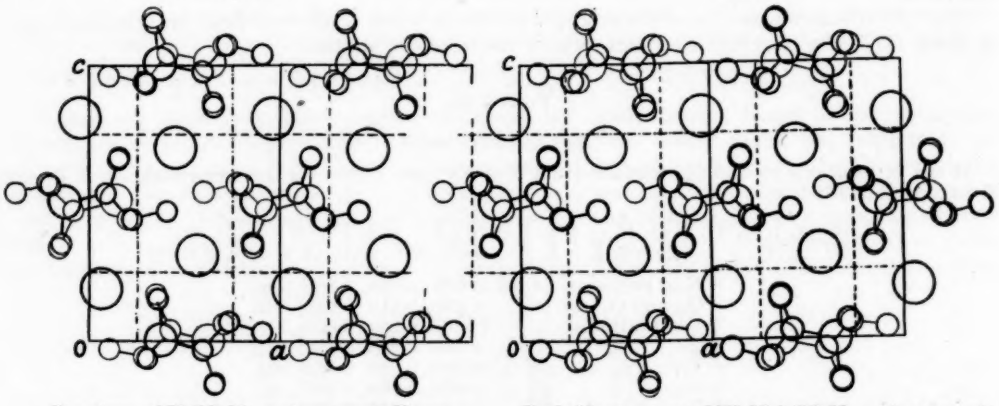
We have not attempted further refinement of the structure analysis of the potassium salt because we do not consider that the accuracy of the structure factors warranted it. It is clear that greater accuracy can be obtained by a detailed study of the isomorphous ammonium salt where the errors due to absorption of X-rays are much smaller, and this work is now in progress.

It was mentioned above that some crystals showed a moderately strong (110) reflexion which is forbidden by the space-groups *Pna* and *Pnma*. In searching for an explanation of this, the effect of added cations was studied. It was found that the addition of ammonium ions produced crystals which did not show a (110) reflexion, whereas a batch of crystals containing sodium and potassium ions in the ratio of approximately 1 : 3 gave strong (110) reflexions and showed on further examination other reflexions forbidden by *Pnma*; the extinctions observed corresponded closely, in fact, to those required by *Pcmn* (or *Pcn*) although a few faint reflexions occurred which were forbidden by *Pcmn* and permitted by *Pnma*. It thus appears that the pure potassium and ammonium salts have the space-group *Pnma*, and from the transitional character of the mixed KNa crystals it is probable that the pure sodium salt (or possibly a 1 : 1 compound $KNaSO_3N_2$) has the space-group *Pcmn* or *Pcn*. (Attempts to prepare crystals of the pure sodium salt have not so far been successful on account of its high solubility.) The 3 : 1 KNa crystals showed no appreciable lattice contraction, nor were there any weak odd layer-lines to indicate the existence of a superlattice.

The transformation of the whole structure from the symmetry *Pnma* to that of *Pcmn* can be brought about with little change in energy, by merely interchanging the y-levels of every other row of anions as in Fig. 6. As the cation positions are very nearly at $y = 0$ and $\frac{1}{4}$, they conform to both space-groups alike, so that no alteration in the cationic lattice is necessary to

bring about the change in symmetry. The replacement of potassium by sodium ions is presumably random.

FIG. 6*a*. FIG. 6*b*.



Structure of $K_2SO_3N_2$: *space-group* Pnma. *Probable structure of* $(K, Na)_2SO_3N_2$: *space-group* Pcmn.

Anions in heavy lines are b/2 *above those in light lines.*

It is noteworthy that apart from the height of the cation peaks the projections along [*y*] will be the same for both arrangements, but the definition of any three-dimensional syntheses would be considerably reduced by the coexistence of the two forms in the specimen examined (*i.e.*, it might easily happen that different domains in the same apparently homogeneous crystal belonged to the different space-groups). The good resolution obtained in the section projection and the sections reproduced in Figs. 4 and 5 make it fairly certain that the crystals on which the structure analysis has been based were of the pure *Pnma* form.

DISCUSSION.

The bond lengths and bond angles of the dinitrososulphite ion as calculated from the atomic co-ordinates are given in Table III (see also Fig. 7). They are estimated as reliable to within ±0·06 A. Some recent bond-length measurements are quoted for comparison, and various calculated values are also given.

TABLE III.

Bond lengths (*in* A.).

Bond.	Obs. values, $K_2SO_3N_2$.	Pauling : * Single bond.	Pauling : * Double bond.	S. and S. : † Single bond.	Gordy : † Double bond.	Other observed values.‡
SO	1·43	1·70	1·49	1·69	1·48	1·44[a], 1·45[b], 1·43[c], 1·44[d]
SN	1·63	1·74	1·54	1·74	1·53	1·57[a]
NN	1·30	1·48	1·28	1·48	1·24	1·26[e]
NO	1·35	1·36	1·18	1·43	1·16	1·25[e]

Bond angles :

N–S–O 106°, 105°	S–N–O 121°	O–N–N 118°
O–S–O 108°, 116°	S–N–N 121°	N–N–O 119°

* Values for single and double bonds according to Pauling (" Nature of the Chemical Bond," 1945) assuming additivity of covalent radii.

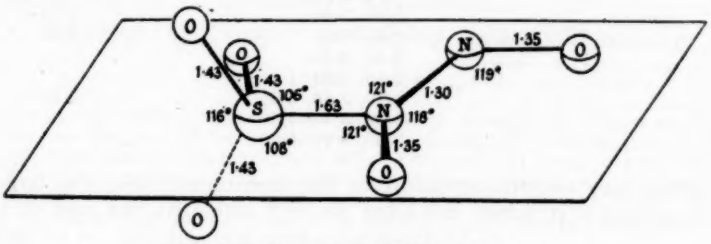
† Values according to Schomaker and Stevenson (*J. Amer. Chem. Soc.*, 1941, **63**, 37) for single bonds, and according to Gordy (*J. Chem. Physics*, 1947, **15**, 81) for double bonds, calculated from more recent bond lengths, and allowing for an electronegativity correction β in the form $r_{AB} = r_A + r_B - \beta|x_A - x_B|$, where x_A and x_B are electro-negativities and $\beta = 0{\cdot}09$ for single and 0·06 for double bonds.

‡ (*a*) $K{\cdot}SO_2{\cdot}NH_2$ (Brown and Cox, *J.*, 1940, 1); (*b*) $SOCl_2$ (Palmer, *J. Amer. Chem. Soc.*, 1938, **60**, 2360); (*c*) SO_2Cl_2 (Palmer, *loc. cit.*); (*d*) β-isoprene sulphone (Cox and Jeffrey, *Trans. Faraday Soc.*, 1942, **38**, 241); (*e*) $(CH_3)_2N{\cdot}NO_2$ (Costain and Cox, *Nature*, 1947, **160**, 826).

The S–O bond length 1·43 A. agrees with those observed in the more reliable investigations of structures containing tetrahedral S–O bonds, and although this is 0·06 A. shorter than the sum of Pauling's covalent double-bond radii, it seems hardly conceivable that more than four

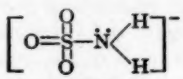
electrons should be involved in each S–O link. It appears then that the value of 1·44 A. should be taken as the upper limit for the length of a pure double bond. From this the double-bond covalent radius of sulphur, r_d^s, can be recalculated by using Gordy's empirical formula, giving $r_d^s = 0{\cdot}90$; if we add 0·10 A., which is the constant difference between single- and double-bond radii in Pauling's table of covalent radii of atoms in the second period, the single-bond radius of sulphur becomes 1·00 A. [cf. 1·02 A. in Me_2S_2 and H_2S_2 (Stevenson and Beach, *J. Amer. Chem. Soc.*, 1938, **60**, 2872) and $(C_2H_4I)_2S_3$ (Dawson and Robertson, *J.*, 1948, 1256)] and the calculated sulphur-to-nitrogen distances become S–N = 1·69 A. and S=N = 1·49 A. These values should be sufficiently reliable to form a basis for discussion of the S–N bond orders in the sulphamate and the nitrososulphite ions.

FIG. 7.

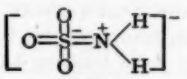


Anion bond-lengths and bond-angles.

The observed length of 1·57 A. for S–N in the $[SO_2{\cdot}NH_2]^-$ ion corresponds to a bond order of about 1·5; thus, having regard to the accuracy achieved in the structure analysis of potassium sulphamate, it is certain that the link cannot adequately be described as either a pure single or a pure double bond. As pointed out by Evans and Gergely (*Nature*, 1948, **162**, 771) in their treatment of the structure of the dinitrososulphite ion itself, the five valency electrons of the nitrogen atom can be regarded as being distributed to form three singly occupied [sp^2] orbitals and a doubly occupied p orbital, so that coplanar single bonds with trigonal symmetry about the nitrogen can be postulated for the S–N and the two N–H bonds; the additional bond strength of the S–N link would then be due to some sharing of the nitrogen p^2 electrons with



(X.)



(XI.)

sulphur. In terms of bond diagrams, the structure can be described as (X) and (XI), both contributing to about the same extent. Unfortunately, there are no intermolecular distances corresponding to NH · · · · · O bridges in potassium sulphamate, which might reveal the directions of the N–H bonds and provide more direct evidence of the nitrogen hybridisation.

In the dinitrososulphite ion, the S–N bond, with a value of 1·63 A., is 0·06 A. longer than in the sulphamate. This may well be significant, indicating that the replacement of the hydrogens by other atoms has diminished the electron density in the S–N link, which now approximates more closely to the pure single S–N bond. Evans and Gergely have accordingly assumed a bond order of unity and, using a molecular orbital method, have given a very satisfactory description of the electronic structure of the N_2O_2 group. As indicated in Table IV, their calculations account very well for the marked double-bond character between the nitrogen atoms, but may possibly over-emphasize the departure of the N–O links from pure single-bond character.

TABLE IV.

Observed and calculated bond lengths.

Bond.	Obs., A.	Calc., A.	Bond order (calc.).
N–N	1·30	1·30	1·72
$N–O_V$	1·36	1·31	1·45
$N–O_{VI}$	1·36	1·31	1·45

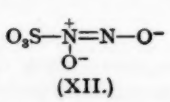
With the proviso that there may be appreciable departures from integral bond orders (which can more appropriately be discussed when the detailed analysis of the ammonium salt has been completed) the best conventional representation of the the ion is (XII).

The co-ordination of the ionic lattice is 12 : 6, and the anions and cations lie in alternate layers with a separation of $y = \frac{1}{4}$. Each anion has 12 cation neighbours arranged in two irregular hexagons, one in the layer above, and the other in the layer below, whereas each cation is co-ordinated to six dinitrososulphite ions, three in each layer above and below. As shown in Table V, the K–O distances lie within the usual range observed in compounds of this type. The K–N distances are considerably greater, and it is interesting to note that the larger separation corresponds to the greater positive charge as calculated by Evans and Gergely.

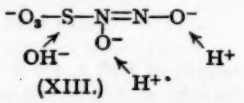
TABLE V.

	$K_2SO_5N_2$.	$K{\cdot}SO_3{\cdot}NH_2$ (Brown and Cox, *loc. cit.*).
KO_I	2·95, 3·00	2·75
KO_{II}	2·85, 3·10	2·96
KO_V	2·80, 3·20	—
KO_{VI}	2·95, 2·95	—
KN_{IV}	3·60, 3·60, 3·95	3·10
KN_{VII}	3·40, 3·40, 3·60	—
KS	3·50, 3·90, 4·00	—

The long controversy over the structure of the dinitrososulphites was largely due to the difficulty of reconciling a structure involving an S–N link with the ease of the qualitative



(XII.)



(XIII.)

decomposition to sulphate and nitrous oxide. Unfortunately, no kinetic measurements of the decomposition of salts in weakly acid solution have been made, but on the basis of the configuration and charge distribution described in this paper, hydrolysis of the S–N link to sulphate and hyponitrous acid can be postulated as in (XIII). As is well known, hyponitrous acid decomposes to nitrous oxide in acid solution.

The potassium salt decomposes rapidly when heated to about 110° (Divers and Haga, *J.*, 1895, **67**, 452) and various amounts of potassium sulphite have been reported in the sulphate product; we have also found that a crystal of the dinitrososulphite may decompose over a period of several months at room temperature, leaving a transparent aggregate of potassium sulphate crystals in which the [*c*] axes tend to be oriented parallel to the [*b*] axis of the original crystal. It is reasonable to suppose that these dry reactions are also due to hydrolysis by traces of water adsorbed on the crystals, a view which is supported by reports that the compound is considerably more stable in a dry, non-acid atmosphere.

EXPERIMENTAL.

For the preparation of potassium dinitrososulphite the method of Weitz and Achterberg (*loc. cit.*) was found to give good yields, but it was necessary to recrystallise from 15% potassium hydroxide at 50° to obtain crystals suitable for *X*-ray analysis; *i.e.*, of 0·1—0·2 mm. diameter and as evenly developed as possible. However, by using a more dilute solution in the preparation, and by leaving it undisturbed during absorption of the nitric oxide, sufficiently large crystals can be obtained directly. The same method of preparation was used for the ammonium salt, whereas crystals of the thallium salt were grown by letting solutions of thallium perchlorate and sodium dinitrososulphite diffuse together into a saturated solution of ether in water. The analyses were: Found, in potassium salt: K, 35·64; S, 14·61 (Calc. for $K_2SO_5N_2$: K, 35·81; S, 14·69%). Found, in thallium salt: Tl, 74·52 (Calc. for $Tl_2SO_5N_2$: Tl, 74·48%).

Photographs were taken with Cu-K_α radiation. The cell dimensions, determined from high-order reflexions by the Straumanis method (Buerger, "*X*-Ray Crystallography," 1942, p. 394), are given on p. 1784. The density of the crystals determined by flotation is 2·56 ± 0·02 g./c.c. (Calc. for 4 molecules per unit cell, 2·54 ± 0·02).

The approximate minimum and maximum refractive indices are $\alpha = 1{\cdot}48$ along [*b*], $\gamma = 1{\cdot}66$ along [*a*].

The intensities of the reflexions were recorded photographically on complete sets of 15° oscillations about [010] and [100], and equi-inclination Weissenberg photographs for all layer-lines with equi-inclination angle $\nu < 20°$. A multiple film technique was used and about 5000 intensity measurements were made visually. These were correlated, corrected for absorption, and multiplied by the appropriate geometrical and polarisation factors, and the relative structure amplitudes of 469 planes were finally derived. For zero layer-line photographs the ordinary absorption correction for cylindrical specimens (Int. Tables, p. 584) was used; in the case of equi-inclination Weissenberg photographs this correction is still valid if the specimen radius r is replaced by $r \sec \nu$. For non-equatorial layer-lines on oscillation photographs of small diameter crystals it was found that a satisfactory correction factor was obtained by taking the mean of factors for specimens of radius r and $r \operatorname{cosec} \phi$ respectively (ϕ = half angle of layer-line cone). The deviations from cylindrical shape, however, and the uncertainty of the

crystal dimensions, make it impossible to calculate the absorption errors accurately, and on this account alone the corrected intensities may be in error by as much as 25% in the worst cases.

We wish to record our indebtedness to the Government Grants Committee of the Royal Society and the Department of Scientific and Industrial Research for financial support, and to Birkbeck College and the University of Leeds for scholarships awarded to one of us (H. P. S.).

We wish to thank Mr. F. J. Garrick and Mr. A. White for assistance with some chemical work, especially the preparation and analysis of the thallium salt.

THE UNIVERSITY, LEEDS, 2. [*Received, January 27th*, 1949.]

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383. *Polarography of Quinoline Derivatives. Part IV. Amperometric Titration of Copper and Zinc with Quinaldinic Acid.*

By JOHN T. STOCK.

The amperometric titration with quinaldinic acid of copper, zinc, and cadmium in concentrations less than 3×10^{-3}M has been studied. Copper and zinc are precipitated slowly in the cold, but the titration is practicable at 60°. Alternatively, excess of the reagent may be added and back-titrated at room temperature with standard copper or zinc solution. Under certain conditions, copper and zinc in the same solution may be successively titrated, and copper may be determined in the presence of cadmium. Attempts to determine cadmium either directly or by back-titration were unsuccessful.

MANY of the selective organic precipitants for metals are polarographically reducible and have been used successfully in amperometric titration (for bibliography, see Kolthoff and Lingane, "Polarography," New York, 1941, pp. 469—472; Stock, *Analyst*, 1947, **72**, 291). Quinaldinic acid, a useful precipitant for copper, etc. (see "Organic Reagents for Metals," Hopkin and Williams, Ltd., London, 1943, p. 122) gives well-defined polarographic reduction waves (Stock, Part I, *J.*, 1944, 427); the present work deals with the use of this reagent in the amperometric titration of copper and zinc in concentrations less than 3×10^{-3}M.

EXPERIMENTAL.

Quinaldinic Acid Solution.—The B.D.H. product was recrystallised twice from benzene, dried at 105°, and used to prepare a 0·025M-stock solution in 50% aldehyde-free alcohol. When necessary, this solution was diluted with the same solvent mixture.

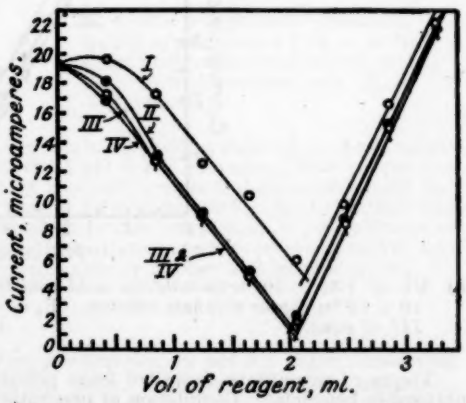
Buffer Solutions.—These were as in Part I, and were examined polarographically for reducible impurities; pH measurements (quinhydrone electrode) were made at room temperature.

Copper, Zinc, and Cadmium Solutions.—0·1M-Stock solutions were prepared from B.D.H. "AnalaR" sulphates and were standardised gravimetrically by precipitation with quinaldinic acid (Rây and Bose, *Z. anal. Chem.*, 1933, **95**, 400). The solutions were diluted as required with the appropriate buffers and sufficient 1% gelatin solution to render them 0·03% with respect to gelatin.

Apparatus.—Three titration cells were used: (*a*) for 20—50-ml. samples, a 100-ml., tall Pyrex beaker fitted with a clamp-on cap (Stock, *Analyst*, 1947, **72**, 291); (*b*) for 5—10-ml. samples, the cell described by Fill and Stock (*Analyst*, 1944, **69**, 178); (*c*) for 0·5—2-ml. samples, an all-glass micro-cell (Stock, *Analyst*, 1946, **71**, 583). A mercury pool anode was used in all experiments. When necessary, the cells were heated in a large beaker of water thermostatically maintained at 60° ± 0·4°.

Applied voltage (E_a) was regulated by a polarising unit (Stock, *ibid.*, p. 585) which incorporated a damping control for the calibrated Cambridge "Spot" galvanometer used to measure the current.

FIG. 1.



10·2 *Ml. of* $2{\cdot}5 \times 10^{-3}$M-*copper sulphate and* 0·03% *of gelatin in pH* 5·0 *buffer at* 60° *titrated with* 25×10^{-3}M-*quinaldinic acid solution.* $E_a = -1{\cdot}2$ *volts. Curve I*, 1 *min. after additions; II*, 3 *mins.; III*, 5 *mins.; IV*, 7 *mins.*

The characteristics of the dropping-mercury electrodes were: (*a*) $m = 0{\cdot}917$ mg. sec.$^{-1}$, $t = 3{\cdot}39$ secs., $m^{2/3}t^{1/6} = 1{\cdot}157$; (*b*) $m = 1{\cdot}511$ mg. sec.$^{-1}$, $t = 3{\cdot}08$ secs., $m^{2/3}t^{1/6} = 1{\cdot}588$, determined on open circuit in 0·1N-potassium chloride at 25°. Most of the measurements were made with electrode (*b*).

General.—Solutions were deoxygenated by a stream of nitrogen which was first passed through a bubbler containing a little of the solution under examination at the same temperature as the sample in the cell. Gas was bubbled through the solution after each addition of reagent and was cut off 1 minute

before reading the galvanometer. In all cases, the current was corrected for the diluting effect of the added reagent (Kolthoff and Lingane, *op. cit.*, p. 450).

Titration of Copper.—In the presence of 0·02—0·03% of gelatin, quinaldinic acid buffered at pH 5 gives a well-defined single wave (Part I). At this pH, precipitation by the reagent of copper, zinc, and cadmium should be virtually complete (Shennan, *Analyst*, 1939, **64**, 14; Flagg and McClure, *J. Amer. Chem. Soc.*, 1943, **65**, 2346). Experiments were accordingly initiated under these conditions.

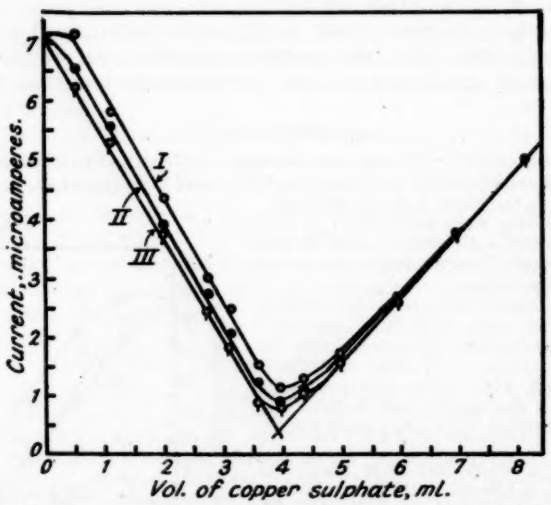
At room temperature, precipitation of copper quinaldinate is slow, and reasonable results are obtainable only if 10 minutes or longer elapse between addition of reagent and the reading of current. Precipitation is more rapid at 60° and the titration then becomes practicable (Fig. 1). Typical results are given in Table I.

TABLE I.

Titration of copper in pH 5·0 buffer containing 0·03% of gelatin with quinaldinic acid solution. Temp. = 60°; E_a = −1·2 *volts. Interval between additions, 5 mins.*

Vol. of sample, ml.	Concns., M × 10^{-3}. Copper.	Reagent.	Titres, ml. Calc.	Obs.	Vol. of sample, ml.	Concns., M × 10^{-3}. Copper.	Reagent.	Titres, ml. Calc.	Obs.
50	2·5	25	10·00	10·04	10	1·0	25	0·80	0·82
44	0·91	20	4·00	3·96	10	0·5	25	0·40	0·42
40	2·5	25	8·00	7·98	1·5	2·5	25	0·300	0·292
25	2·0	25	4·00	4·01	0·9	1·0	5	0·360	0·355, 0·360, 0·357
10	2·5	25	2·00	1·99, 2·00, 1·98	0·9	0·5	5	0·180	0·176
10	2·0	25	1·60	1·59	0·9	0·25	5	0·090	0·092
10	1·5	25	1·20	1·20, 1·19					

FIG. 2.



44 *Ml. of* 1·82 × 10^{-3}M-*quinaldinic acid and* 0·03% *of gelatin in pH* 4·9 *buffer at* 14° *titrated with* 10 × 10^{-3}M-*copper sulphate solution.* E_a = −1·2 *volts. Curve I*, 1 *min. after additions*; *II*, 3 *mins.*; *III*, 5 *mins.*

Traces of precipitate deposited from previous titrations on the burette-tip, cell walls, etc., were noticeably beneficial. Completion of precipitation was most rapid in the smallest cell, which had the lowest ratio of volume to wetted area.

Reversing the procedure, *i.e.*, placing the copper-containing solution in the burette, also facilitates the precipitation. The titration then becomes practicable at room temperature (Fig. 2). Advantageous both in assisting precipitation and in avoiding continual change of solution in the burette is the addition to the buffered copper-containing solution of a known but excess volume of the reagent, followed by back-titration at room temperature with standard copper solution. Typical results are given in Table II.

Titration of Zinc.—Since the solubility product of zinc quinaldinate is higher than that of the copper compound (Flagg and McClure, *loc. cit.*), the titration curves of zinc (E_a = −1·4 volts) are more rounded near the end-point than are those of copper (cf. Kolthoff and Lingane, *op. cit.*, p. 458). Apart from this and except for more sluggish precipitation, zinc solutions buffered at pH 5 behaved similarly to those of copper and, except at the lowest concentrations, gave results of similar accuracy.

TABLE II.

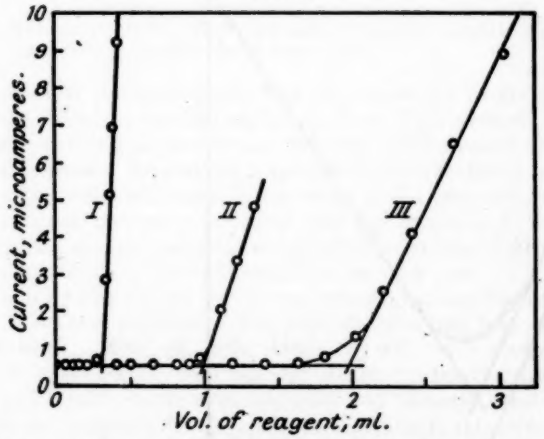
Back-titration of 5 ml. of 5 × 10^{-3}M-quinaldinic acid added to copper-containing solutions buffered at pH 5·0 with 2·5 × 10^{-3}M-copper sulphate solution. Temp. = 14—16°; E_a = −1·2 *volts. Interval between additions, 5 mins.*

Vol. of sample, ml.	Copper concn., M × 10^{-3}.	Titres, ml. Calc.	Obs.
5	0	5·00	5·02
5	1	3·00	3·02, 3·02
5	1·5	2·00	1·99, 1·97
5	2·0	1·00	1·00
0·3 *	2·5	0·600	0·581

* 0·9 Ml. of reagent added.

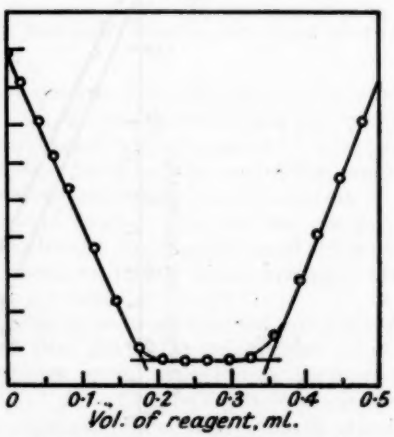
At this pH, with an applied voltage of −1·06, the diffusion current of quinaldinic acid, but not that of zinc, is obtained. The titration curves of zinc with quinaldinic acid are then of the "reversed L" form shown in Fig. 3.

FIG. 3.



Zinc sulphate and 0·03% of gelatin in pH 5·0 buffer at 60° titrated with 25 × 10^{-3}M-quinaldinic acid solution. E_a = −1·06 *volts. Curve I, 1·5 ml., 2·5 × 10^{-3}M with respect to zinc; II, 10 ml., 1·25 × 10^{-3}M; III, 10 ml., 2·5 × 10^{-3}M.*

FIG. 4.



1·8 Ml. of pH 5·0 buffer at 60° containing 0·03% of gelatin and 1·25 × 10^{-3}M of both copper and zinc titrated with 25 × 10^{-3}M-quinaldinic acid. E_a = −1·06 *volts.*

Stepwise Titration of Copper and Zinc.—The difference in solubility product referred to above causes preferential precipitation of copper when a solution buffered at pH 5 and containing both copper and zinc is titrated with quinaldinic acid. If the applied voltage is −1·06, copper and quinaldinic acid, but not zinc, give diffusion currents, and the titration curve has the form shown in Fig. 4 (cf. Kolthoff and Pan, *J. Amer. Chem. Soc.*, 1939, **61**, 3402). The first break indicates completion of precipitation of copper, the second that of zinc. The results given in Table III indicate no serious co-precipitation, and may permit the development of a method for the micro-titration of brasses and similar alloys.

TABLE III.

Stepwise titration with 25 × 10^{-3}M-quinaldinic acid of copper and zinc in pH 5·1 buffer containing 0·03% of gelatin. Temp. = 60°; E_a = −1·06 *volts. Interval between additions, 5 mins.*

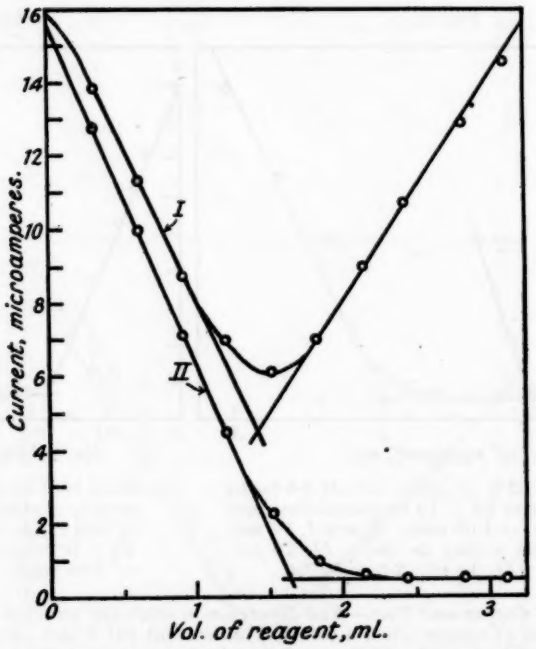
Vol. of sample, ml.	Concns., M × 10^{-3}. Cu.	Zn.	Titres, ml. Copper. Calc.	Obs.	Zinc. Calc.	Obs.
44	0·568	0·568	2·00	1·97	2·00	2·03
25	2·0	0·5	4·00	4·02	1·00	1·01
10	1·5	1·0	1·20	1·18, 1·19	0·80	0·85, 0·82
10	1·0	1·5	0·80	0·81, 0·79	1·20	1·15, 1·18
10	0·5	2·0	0·40	0·38	1·60	1·61
1·8	1·25	1·25	0·180	0·182	0·180	0·169
1·0	1·5	1·0	0·120	0·116	0·080	0·081

Titration of Cadmium.—Shennan (*loc. cit.*) has shown that, under gravimetric conditions, cadmium is completely precipitated by quinaldinic acid in the pH range 3·9—7·2. Attempted titration with quinaldinic acid of pH 5 buffers containing up to $2·5 \times 10^{-3}$M of cadmium showed that the precipitate was very slow in appearing at 60°. With an applied voltage of −0·9 (cadmium, but not the reagent, reduced), equilibrium is not established even with 10 minutes between additions of reagent, and after the theoretical titre had been exceeded by 100%. With an applied voltage of −1·2, the current *increased* irregularly from the first addition of reagent.

Since increased pH should reduce the solubility of the precipitate (Flagg and McClure, *loc. cit.*), experiments were repeated in a borate buffer of pH 7·1. Both addition of the reagent to the cadmium-containing solution and the reverse gave unsatisfactory results.

Titration of Copper in the Presence of Cadmium.—Although the completeness of the separation has been questioned (Shennan, *loc. cit.*; Lindsey and Shennan, *Analyst*, 1940, **65**, 636), the accurate gravimetric determination of copper as quinaldinate in the presence of cadmium has been reported (Rây and Bose, *loc. cit.*; Majumdar, *Analyst*, 1939, **64**, 874; Pritchard and Chirnside, *ibid.*, 1943, **68**, 244; see also Flagg and McClure, *loc. cit.*). According to Majumdar (*loc. cit.*), separation is possible in the pH range 1·22—2·15. The behaviour of dilute copper solutions buffered at pH 2·1 was therefore investigated. Typical titration curves are shown in Fig. 5. The pronounced rounding of the curves

FIG. 5.



10 *Ml. of* 2×10^{-3}M-*copper sulphate and* 0·03% *of gelatin in pH* 2·1 *buffer at* 60° *titrated with* 25×10^{-3}M-*quinaldinic acid solution. Curve I,* $E_a = -0·8$ *volt; II,* $E_a = -0·4$ *volt.*

near the end-point shows that the more acid conditions increase the solubility of the precipitate (cf. Lindsey and Shennan, *loc. cit.*). Low results are obtained by operating at −0·8 volt (curve I), but the "L" curves obtained with an applied voltage of −0·4 (curve II) give nearly theoretical titres (Table IV), not affected by the presence of cadmium.

TABLE IV.

Titration of 10-*ml. portions of pH* 2·1 *buffers containing copper, cadmium, and* 0·03% *of gelatin with* 25×10^{-3}M-*quinaldinic acid solution. Temp.* = 60°; $E_a = -0·4$ *volt. Interval between additions,* 5 *mins.*

Concns., M × 10^{-3}.		Titres, ml.		Concns., M × 10^{-3}.		Titres, ml.	
Cu.	Cd.	Calc.	Obs.	Cu.	Cd.	Calc.	Obs.
2	0	1·60	1·57, 1·59	2	1	1·60	1·57, 1·59
1·5	0	1·20	1·17	2	2	1·60	1·61
1	0	0·80	0·83	2	3	1·60	1·63
2	0·5	1·60	1·57	2	5	1·60	1·59

Manganese, nickel, and cobalt, in concentrations similar to that of cadmium, likewise do not interfere with the titration of copper under these conditions.

Titration of Copper and Zinc in the Presence of Ferrous Iron.—Addition of quinaldinic acid to a pH 5 buffer at 60° containing ferrous iron and 0·03% of gelatin gives an intense red colour (Rây and Bose, *loc. cit.*). With an applied voltage of −1·2, the current increases linearly with the volume of reagent added. Titration of copper under these conditions, in the presence of up to 1×10^{-3}M of ferrous iron, gives good results. On the other hand, addition of excess of reagent and its back-titration with standard copper solution is unsatisfactory; the colour of the precipitate indicates pronounced co-precipitation of iron.

In the case of zinc, poor results due to pronounced co-precipitation of iron are obtained in both modes of titration.

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384. *The Condensation of* N-*Substituted Maleimides with Thioureas.*

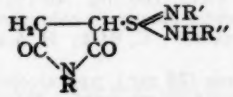
By D. H. Marrian.

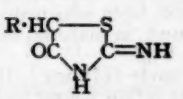
N-Substituted maleimides condense readily with thiourea, *N*-phenylthiourea, and with thiocarbanilide. The products, which are additive in molecular formula, are shown to be probably thiazolidones of type (III).

To further the investigation of the reactivity of maleimides towards free thiol groups (Friedmann, Marrian, and Simon-Reuss, *Brit. J. Pharmacol.*, 1949, **4**, 105; Marrian, this vol., p. 1515) it was decided to investigate whether these imides would react with the incipient thiol group of thioureas. Equimolar solutions of the reactants readily deposited the crystalline products in good yield, although in the case of the more insoluble phenyl-substituted thioureas it was sometimes necessary to carry out the reaction in boiling alcohol. All the six compounds obtained analysed as addition products and were neutral, thereby eliminating one of the possible structures (I), which is that of a mono-acid base. Furthermore, Raney-nickel desulphurisation in boiling alcohol did not give a substituted succinimide (cf. Marrian, *loc. cit.*).

A second possibility was that the reaction was analogous to that reported by Andreasch (*Monatsh.*, 1895, **16**, 789; 1897, **18**, 56), who showed that simple or substituted thioureas with unsaturated dicarboxylic acids or their anhydrides gave thiazolidones such as (II; R = $CH_2 \cdot CO_2H$) from maleic acid and thiourea, and (II; R = $CHMe \cdot CO_2H$) from citraconic acid or anhydride.* Compounds of structure (II) were originally prepared by Volhard (*Annalen*, 1873, **166**, 383) and Maly (*ibid.*, 1873, **168**, 133) by condensation of chloroacetic acid with thiourea, and their structure as thiazolidones or ψ-thiohydantoins was elucidated by Liebermann and Lange (*Ber.*, 1879, **12**, 1588). The unambiguous synthesis of (II; R = $CH_2 \cdot CO_2H$) from thiomalic acid and cyanamide (Andreasch, *loc. cit.*) completed the structural evidence for (II). This is an argument in favour of a structure such as (III) for the products from *N*-substituted maleimides and thioureas, and (III) is supported by the nature of the products of desulphurisation which are all substituted succindiamides (IV) formed by fission of (III) along the broken line. The six-membered-ring structure corresponding to (III) is less likely although the present work does not eliminate it.

A third possibility, that the compounds might be substituted pyrimidines [cf. the reaction reported by Erlenmeyer and Heitz (*Helv. Chim. Acta*, 1942, **25**, 832) between cinnamic acid and thiourea], can be dismissed on the evidence of desulphurisation.


(I.)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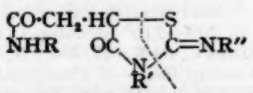
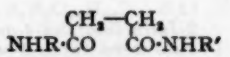

(III.)

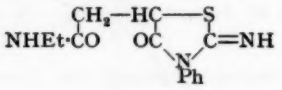

(IV.)

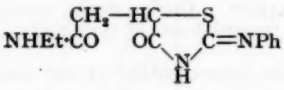
From aqueous-alcoholic solutions of *N*-ethylmaleimide and thiourea at room temperature was isolated 2-*iminothiazolid*-4-*one*-5-*acetoethylamide* (III; R = Et; R′ = R″ = H) which furnished, on treatment with Raney nickel, N-*ethylsuccindiamide* (IV; R = Et; R′ = H), also prepared by ammonolysis of *N*-ethylsuccinimide in alcohol. Similarly from *N*-ethylmaleimide and *N*-phenylthiourea was isolated 2-*imino*-3-*phenylthiazolid*-4-*one*-5-*acetoethylamide*

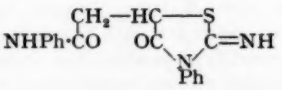
* Bougault and Chabrier (*Compt. rend.*, 1947, **224**, 656) have shown that benzoylacrylic acid and thiourea react analogously.

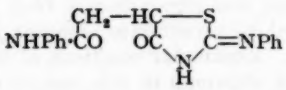
(III; R = Et; R′ = Ph; R″ = H), and from thiocarbanilide, 2-*anilo*-3-*phenylthiazolid*-4-*one*-5-*acetoethylamide* (III; R = Et; R′ = R″ = Ph), both of which gave N-*phenyl*-N′-*ethylsuccindiamide* (IV; R = Et; R′ = Ph) on desulphurisation. The structure of the latter diamide was proved by synthesis from maleic acid monoethylamide by catalytic hydrogenation to N-*ethylsuccinamic acid*, which with thionyl chloride and aniline gave (IV; R = Et; R′ = Ph). The series from *N*-phenylmaleimide differed in only one respect: the compounds formed by the imide with thiourea and *N*-phenylthiourea gave the same desulphurised product, the known *N*-phenylsuccindiamide (IV; R = Ph; R′ = H) (Menschutkin, *Annalen*, 1872, **162**, 182), whilst that from thiocarbanilide gave the known succindianilide (IV; R = R′ = Ph) (*idem*, *ibid.*, p. 187). The products are therefore 2-*iminothiazolid*-4-*one*-5-*acetanilide* (III; R = Ph; R′ = R″ = H) from *N*-phenylmaleimide and thiourea, 2-*anilothiazolid*-4-*one*-5-*acetanilide* (III; R = R″ = Ph; R′ = H) from *N*-phenylmaleimide and *N*-phenylthiourea, and 2-*anilo*-3-*phenylthiazolid*-4-*one*-5-*acetanilide* (III; R = R′ = R″ = Ph) from *N*-phenylmaleimide and thiocarbanilide.

The Raney-nickel treatment is seen to lead to breakdown of the molecule further than the dethio-stage. In the case of (III; R = Et; R′ = R″ = H), ammonia (identified as the picrate) was isolated from the effluent gases.

(V*a*.) 

 (V*b*.)

(VI*a*.) 

 (VI*b*.)

A point of interest arises in the products from both imides and *N*-phenylthiourea. In both cases, two formulations are possible (V*a* and *b*) from *N*-ethylmaleimide and (VI*a* and *b*) from *N*-phenylmaleimide. In each case only one isomer was isolated, (V*a*) in quantitative crude yield, and (VI*b*) in 69% crude yield. The melting points of the crude products were not raised by recrystallisation, so that mixtures were, in all probability, not formed.

Experimental.

2-*Iminothiazolid*-4-*one*-5-*acetoethylamide*.—*N*-Ethylmaleimide (5 g.) in alcohol (40 c.c.) and water (80 c.c.) was added to thiourea (3·04 g.) in alcohol (20 c.c.) and water (40 c.c.), and the mixture kept overnight at room temperature. Scratching caused crystallisation of the *product* (5·58 g., 69·5%), m. p. 195—196°. For analysis, the material was recrystallised from water, giving colourless prisms, m. p. unchanged (Found, in material dried at 80°: C, 41·3; H, 5·8; N, 20·5. $C_7H_{11}O_2N_3S$ requires C, 41·8; H, 5·5; N, 20·9%). The low value for carbon and the high value for hydrogen are due doubtless to the extremely hydroscopic nature of the dried material, which readily forms the *monohydrate* (Found: C, 38·6; H, 6·0; loss at 120°, 7·7. $C_7H_{11}O_2N_3S,H_2O$ requires C, 38·4; H, 6·0; H_2O, 8·2%).

2-*Imino*-3-*phenylthiazolid*-4-*one*-5-*acetoethylamide*.—*N*-Ethylmaleimide (125 mg.) and *N*-phenylthiourea (152 mg.) in alcohol (4 c.c.) were warmed until dissolution was complete, whereupon a yellow colour developed; after 3 days, the crystalline solid was filtered off and washed with alcohol [quantitative yield, m. p. 237° (decomp.) after sintering at 235°]. After one recrystallisation from dioxan and one from a large volume of water (90 mg. in 200 c.c.) the *amide* formed colourless prisms, m. p. 235° (decomp.) (Found, in material dried at 80°: C, 56·1; H, 5·4; N, 14·6. $C_{13}H_{15}O_2N_3S$ requires C, 56·3; H, 5·4; N, 15·2%).

2-*Anilo*-3-*phenylthiazolid*-4-*one*-5-*acetoethylamide*.—*N*-Ethylmaleimide (125 mg.), thiocarbanilide (228 mg.), and alcohol (8 c.c.) were heated under reflux for 2 hours and then kept overnight. Scratching yielded colourless prisms which were filtered off and washed with alcohol: yield, 160 mg. (46·7%); m. p. 204—205° (decomp.). Recrystallised from alcohol, from which it separates slowly in colourless prisms, the *product* had m. p. 209—210° (decomp.) (Found, in material dried at 80°: C, 64·4; H, 5·4; N, 12·5. $C_{19}H_{19}O_2N_3S$ requires C, 64·6; H, 5·4; N, 11·9%).

2-*Iminothiazolid*-4-*one*-5-*acetanilide*.—*N*-Phenylmaleimide (176 mg.), thiourea (76 mg.), and alcohol (10 c.c.) were warmed on the steam-bath until the initial yellow colour had almost disappeared. When the mixture was cooled, a colourless crystalline powder was deposited (180 mg., 71·5%), m. p. 223—223·5° (decomp.) (depending on the rate of heating). The *anilide* crystallised from alcohol (20 c.c.) in colourless prisms, m. p. 220—221° (decomp.) (Found, in material dried at 80°: C, 52·8; H, 4·5; N, 17·5. $C_{11}H_{11}O_2N_3S$ requires C, 53·0; H, 4·4; N, 16·9%).

2-*Anilothiazolid*-4-*one*-5-*acetanilide*.—*N*-Phenylmaleimide (1·76 g.), *N*-phenylthiourea (1·52 g.), and alcohol (40 c.c.) were heated under reflux for 2 hours and then set aside overnight. The colourless crystalline precipitate was filtered off and washed with alcohol, giving 2·26 g. (69%) of colourless prisms, m. p. 216·5—217·5° (decomp.). Recrystallisation from alcohol did not change the m. p. (Found, in material dried at 80°: C, 62·6; H, 4·5; N, 12·9. $C_{17}H_{15}O_2N_3S$ requires C, 62·8; H, 4·6; N, 12·9%).

2-*Anilo*-3-*phenylthiazolid*-4-*one*-5-*acetanilide*.—*N*-Phenylmaleimide (0·88 g.), thiocarbanilide (1·14 g.), and alcohol (30 c.c.) were heated under reflux for 2 hours and then allowed to cool. Scratching

readily caused crystallisation of the *anilide* in almost colourless prisms (1·05 g., 52%), m. p. 206—208° (decomp.). A second crop (0·28 g.), m. p. 203—205° (decomp.), was obtained by evaporation of the mother-liquors. Two recrystallisations from alcohol gave colourless matted needles, m. p. 209—210° (decomp.) (Found, in material dried at 80°: C, 68·8; H, 5·0; N, 9·8. $C_{22}H_{19}O_4N_3S$ requires C, 68·8; H, 4·7; N, 10·5%).

Desulphurisation Experiments.—The addition product (1·0 g.), Raney nickel (" 15 c.c."), and alcohol (*ca.* 40 c.c.) were heated under reflux for some 20 hours, the nickel was extracted for about the same time with hot alcohol, and the extract filtered and evaporated to incipient crystallisation.

(*a*) 2-Iminothiazolid-4-one-5-acetoethylamide gave colourless plates (110 mg.), m. p. 175·5—177°, and a further 130 mg. of slightly lower-melting material. Recrystallised from alcohol, *N-ethylsuccindiamide* formed colourless prisms, m. p. 175·5—176·5° (Found, in material dried at 80°: C, 50·3; H, 8·4; N, 18·4. $C_6H_{12}O_2N_2$ requires C, 50·0; H, 8·3; N, 19·4%), identified by the following synthesis. *N*-Ethylsuccinimide (2·5 c.c.; Menschutkin, *Annalen*, 1876, **182**, 90) and alcoholic ammonia solution (50 c.c., saturated at 0°) were heated in a stoppered bottle at 105° overnight. The solution was evaporated *in vacuo*, and the residue recrystallised twice from alcohol to m. p. 174—175°, undepressed on admixture with the desulphurised product described above. The yield was low.

In one such degradation, a stream of nitrogen was blown through the reaction mixture, and the effluent gases passed through an alcoholic solution of picric acid. A precipitate formed which decomposed on heating at 269—284°·alone or admixed with an authentic sample of ammonium picrate.

(*b*) 2-Imino-3-phenylthiazolid-4-one-5-acetoethylamide gave *N-phenyl-N'-ethylsuccindiamide* (365 mg.) in colourless needles, m. p. 170—171°, unchanged by recrystallisation from alcohol. 2-Anilo-3-phenylthiazolid-4-one-5-acetoethylamide gave 220 mg. of the same product (Found, in material dried at 80°: C, 65·7; H, 7·3; N, 12·4. $C_{12}H_{16}O_2N_2$ requires C, 65·5; H, 7·3; N, 12·7%). It was identified by the following synthesis.

Maleic acid monoethylamide (14·3 g.) was hydrogenated in 95% alcohol (125 c.c.) at atmospheric pressure over platinum oxide (uptake, 2340 c.c. in 2¼ hours, inclusive of reduction of the catalyst). The filtered solution was boiled under reflux with charcoal, filtered, and evaporated *in vacuo*. The residue crystallised (15·2 g., inclusive of some oil; quantitative crude yield). The solid was pressed dry on a porous plate and recrystallised from ethyl acetate, giving *N-ethylsuccinamic acid* as colourless needles (8·4 g.), m. p. 93·5—95·5°; two further recrystallisations from the same solvent raised the m. p. to 95—96° (Found, in material dried at room temperature: C, 49·7; H, 7·5; N, 9·7; equiv., 143. $C_6H_{11}O_3N$ requires C, 49·7; H, 7·6; N, 9·6%; equiv., 145).

N-Ethylsuccinamic acid (1·45 g.) was dissolved in aniline (5 c.c.), cooled in a water-bath, and treated dropwise with thionyl chloride (0·75 c.c.) with manual shaking. The reaction flask was loosely stoppered and left at room temperature for 2 hours. The reaction mixture was dissolved in 5N-hydrochloric acid, and the solution extracted continuously with ether overnight. *N*-Phenyl-*N'*-ethylsuccindiamide separated from the ethereal extract on cooling (0·32 g.; m. p. 147—154°). Recrystallisation from water gave colourless needles, m. p. 171—171·5°. Evaporation of the ethereal mother-liquors gave a further 0·72 g. of impure material.

(*c*) 2-Iminothiazolid-4-one-5-acetanilide gave colourless prisms (0·31 g.), m. p. 175·5—176°, raised to 177—179° by two recrystallisations from alcohol, whilst 2-anilothiazolid-4-one-5-acetanilide gave 210 mg. of the same compound, which was identified as *N*-phenylsuccindiamide by mixed m. p. and by analysis (Found, in material dried at 80°; C, 62·6; H, 6·5; N, 14·5. Calc. for $C_{10}H_{12}O_2N_2$: C, 62·5; H, 6·2; N, 14·6%).

(*d*) 2-Anilo-3-phenylthiazolid-4-one-5-acetanilide gave succindianilide (300 mg.), m. p. 195—196° (raised to 223—224° by recrystallisation from alcoholic potassium hydroxide), identified by mixed m. p. with an authentic specimen, m. p. 224—225°.

The author thanks Prof. J. S. Mitchell and Dr. E. Friedmann, of this Department, for their interest, and Mr. L. Callaghan for technical assistance.

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University of Cambridge.

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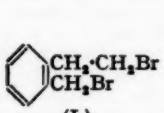
385. *The Synthesis and Properties of 2:7-Disubstituted 1:2:3:4-Tetrahydroisoquinolines.*

By M. H. Beeby and Frederick G. Mann.

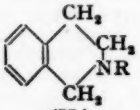
The synthesis of *5-nitro-2-2'-chloroethylbenzyl chloride* by the chloromethylation of 2-*p*-nitrophenylethyl chloride, and the parallel synthesis of *5-nitro-2-2'-bromoethylbenzyl bromide* are described. These compounds condense readily with primary amines to give the corresponding 7-nitro-2-aryl(or -alkyl)-1:2:3:4-tetrahydroisoquinolines. Reduction leads to the 7-amino-compounds, and other derivatives can thus be prepared.

It has been shown by Holliman and Mann (*J.*, 1942, 737) that *o*-2-bromoethylbenzyl bromide (I) can be obtained in a five-stage synthesis from *o*-toluidine, and is thus reasonably readily available. These workers showed also that the dibromide condensed readily with primary amines to give 2-substituted 1:2:3:4-tetrahydroisoquinolines (II) (*J.*, 1945, 34), and with sulphonamides to give the 2-sulphonyltetrahydroisoquinolines (III); furthermore the dibromide could

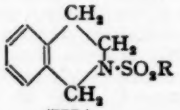
be condensed with alkyl (and aryl) dichloroarsines by the action of sodium to give the 2-substituted 1 : 2 : 3 : 4-tetrahydro*iso*arsinolines (IV) (*J.*, 1943, 547). It is noteworthy however that none of the compounds of type (II), (III), or (IV) has any marked physiological activity. It appeared probable that the prime cause of this therapeutic inactivity was the absence of substituents in the *o*-phenylene ring.



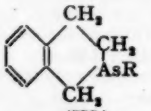
(I.)



(II.)

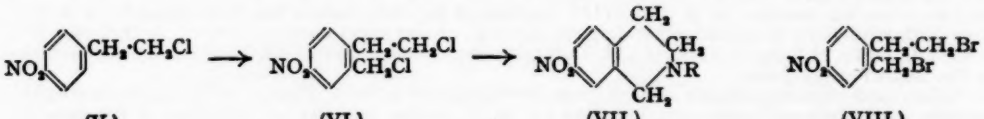


(III.)



(IV.)

The various stages in the above synthesis of the dibromide (I) preclude any practicable modification whereby a substituent could be introduced into the ring, and an entirely different synthetic route was thus required. For this purpose, therefore, 2-phenylethyl alcohol was converted into the chloride, which on nitration furnished 2-*p*-nitrophenylethyl chloride (V).



(V.) (VI.) (VII.) (VIII.)

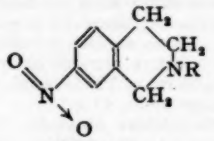
When treated with *s*-dichlorodimethyl ether in the presence of fuming sulphuric acid, (V) underwent smooth chloromethylation to give the crystalline *5-nitro-2-2′-chloroethylbenzyl chloride* (VI). The nature and position of the substituents in the compound (V) leave little doubt that the chloromethyl group has entered the position indicated in (VI), particularly as Stephen, Short, and Gladding (*J.*, 1920, **117**, 510) have proved that the chloromethylation of *p*-nitrotoluene gives 5-nitro-2-methylbenzyl chloride. The orientation of the substituents in the compound (VI) was, however, confirmed by the fact that this compound, when heated with various primary aryl amines and potassium carbonate in a suitable solvent, readily gave the corresponding 7-nitro-2-aryl-1 : 2 : 3 : 4-tetrahydro*iso*quinoline (VII), a condensation precisely similar to that given by the dibromide (I). For example, when the dichloride (VI) and *p*-toluidine in equimolecular quantities were boiled together in *n*-butyl alcohol in the presence of potassium carbonate, condensation occurred to form *7-nitro*-2-p-*tolyl*-1 : 2 : 3 : 4-*tetrahydro*isoquinoline (VII; R = C_6H_4Me); this compound, when reduced in the presence of a platinum catalyst, gave the corresponding *7-amino*-2-p-*tolyltetrahydro*isoquinoline, which was converted in turn into the *7-acetamido-*, *7-benzamido-*, and *7-benzenesulphonamido*-derivatives. A similar mixture of the dichloride, 3 : 4-dimethoxyaniline hydrochloride, and potassium carbonate in boiling *n*-propyl alcohol gave *7-nitro*-2-(3′ : 4′-*dimethoxyphenyl*)-1 : 2 : 3 : 4-*tetrahydro*isoquinoline [VII; R = $C_6H_3(OMe)_2$], which was similarly reduced to the *7-amino*-derivative.

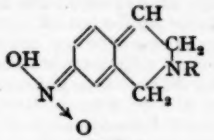
This condensation was not limited to arylamines. A mixture of the dichloride and *n*-butylamine in boiling ethyl alcohol gave ultimately 7-nitro-2-*n*-butyltetrahydro*iso*quinoline (VII; R = Bu^n) as the *hydrochloride*, and diethylaminoethylamine similarly gave 7-nitro-2-2′-diethylaminoethyltetrahydro*iso*quinoline (VII; R = $CH_2·CH_2·NEt_2$) as the *dihydrochloride*.

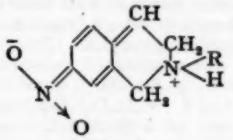
The use of the dichloride (VI) in these syntheses had however one disadvantage, inasmuch as efficient condensation with each primary amine investigated appeared to depend greatly on the temperature, and hence on the solvent, employed; consequently several solvents had to be tested for each amine before optimum conditions could be attained with reasonable certainty. To avoid this difficulty, the more reactive dibromide, corresponding to the dichloride (VI), was similarly prepared, 2-*p*-nitrophenylethyl bromide being treated with *s*-dibromodimethyl ether to give *5-nitro-2-2′-bromoethylbenzyl bromide* (VIII). This reacted readily with primary amines in boiling ethyl alcohol in the presence of potassium carbonate, and the use of solvents of higher b. p. now became unnecessary. Thus condensation under these conditions with *p*-chloroaniline gave *7-nitro*-2-p-*chlorophenyltetrahydro*isoquinoline (VII; R = C_6H_4Cl), which in turn furnished the *7-amino-* and the *7-acetamido*-derivatives, and condensation with *p*-aminoacetanilide gave *7-nitro*-2-p-*acetamidophenyltetrahydro*isoquinoline (VII; R = $C_6H_4·NHAc$), which was also reduced to the *7-amino*-derivative.

In considering the constitution of the above compounds, it is noteworthy that all the 7-nitro-2-aryl(or -alkyl)-tetrahydro*iso*quinolines were coloured (yellow, orange, or red); this colour is clearly associated with the nitro-group, since all the corresponding 7-amino-compounds

were colourless. Furthermore, these coloured 7-nitrotetrahydro*iso*quinolines form colourless crystalline hydrochlorides. There are theoretically three possible structures for a 7-nitro-2-aryl(or -alkyl)-tetrahydro*iso*quinoline (VII). It might possess a normal nitro-group as in


(VII-A.)


(VII-B.)


(VII-C.)

(VII-A), or exist in the *aci*-form (VII-B), or the latter might give the zwitterion (VII-C). Now it is unlikely that the introduction of one normal nitro-group (VII-A) into the otherwise colourless tetrahydro*iso*quinoline would cause this marked development of colour. An interesting compound for direct comparison in this respect would be 7-nitro*iso*quinoline, where the nitro-group must retain its normal structure; this compound is apparently unknown, however, but 7-nitroquinoline, to which the same argument applies, is a colourless crystalline compound (Bacharach, Haut, and Caroline, *Rec. Trav. chim.*, **1933**, **52**, 416). Moreover, if the 7-nitro-derivatives had the structure (VII-A), there is no obvious structural change that would accompany salt formation and cause the disappearance of the orange colour of the above.

It appears probable therefore that our 7-nitro-bases have the quinonoid structure (VII-B), or (VII-C), either of which would almost certainly be coloured, and that the presence of acids suppresses *aci*-formation, so that salts with strong acids (such as the hydrochloride) are salts of the normal form (VII-A). It would be expected that compounds having the highly polar structure (VII-C) would also have comparatively high m. p.s. The fact that both our 2-alkyl derivatives are mobile liquids which give no indication of crystallisation provides some evidence (although far from decisive) that they may have the less polar *aci*-structure (VII-B) rather than the zwitterion structure (VII-C).

The therapeutic activity of several of the above compounds is now being tested.

Experimental.

All the 7-substituted derivatives described below melted with preliminary darkening, the onset and degree of which depended on the particular compound concerned; the m.p.s were therefore determined in a preheated bath. All the 7-amino-compounds were unstable when exposed to light and air, usually rapidly developing a yellowish-brown coloration; the 7-acetamido-compounds behaved similarly, but the colour developed less rapidly.

Synthesis of 5-Nitro-2-2′-chloroethylbenzyl Chloride (VI).—(i) *2-Phenylethyl chloride.* This and the following compound were prepared by Barger (*J.*, 1909, **95**, 2193), who gave only brief details, particularly for the nitro-derivative; we have advantageously modified both preparations. 2-Phenylethyl alcohol (250 g.) was added over a period of 1 hour to a cold well-stirred mixture of phosphorus pentachloride (450 g.) and chloroform (1 l.), which was subsequently heated under reflux for 1·5 hours. The chloroform and most of the phosphorus oxychloride were then removed by distillation, and water was cautiously added to the cold residual liquid to hydrolyse the remaining oxychloride. The product was filtered under gentle suction to decrease emulsification and thus to obtain two well-defined layers. The chloride was separated, taken up in ether, thoroughly washed with water, dried (Na_2SO_4), and distilled; b. p. 112—116°/63 mm. Yield, 230—240 g.

The compound was also efficiently prepared by the action of thionyl chloride on the alcohol.

(ii) *2-p-Nitrophenylethyl chloride.* 2-Phenylethyl chloride (250 g.) was added dropwise during 1 hour to a well-stirred mixture of fuming nitric acid (400 c.c.) and concentrated nitric acid (300 c.c.), cooled in ice and water. The stirring was then continued for 5 hours without external cooling, and the reaction mixture poured into much ice–water and set aside overnight. The mixture of crystals and oil which separated was taken up in ether, and the solution washed with water and dried (Na_2SO_4), and the solvent removed. The yellow residual oil, when placed in a refrigerator overnight, deposited crystals of the *p*-nitro-compound, which were collected, washed with light petroleum, and thoroughly pressed between absorbent paper. The product thus obtained (105 g.) had m. p. 46—48° and, although still contaminated with traces of the *o*-nitro-isomer, was sufficiently pure for the next stage. The filtrate from the residual yellow oil was distilled *in vacuo*; the higher-boiling fraction crystallised on cooling, to yield a second crop of the *p*-nitro-compound; however, the average yield (20 g.) of this crop hardly justifies the time and labour expended.

(iii) s-*Dichlorodimethyl ether.* This was prepared essentially by the method of Descudé (*Bull. Soc. chim.*, 1906, **35**, 956), phosphorus trichloride (540 g.) being slowly added down a condenser to a vigorously agitated mixture of paraformaldehyde (540 g.) and zinc chloride (30 g.) in a 2-l. flask. When the vigorous reaction had subsided, the viscous mixture was distilled under reduced pressure until the temperature of the oil-bath reached *ca.* 140° and paraformaldehyde crystallised in the condenser. The crude distillate was sufficiently pure for the next stage.

The ether was more rapidly prepared by the method of Norris (*Ind. Eng. Chem.*, 1919, **11**, 817), but

the product on initial testing appeared to give much lower yields at the subsequent chloromethylation stage.

(iv) *5-Nitro-2-2′-chloroethylbenzyl chloride.* 2-*p*-Nitrophenylethyl chloride (50 g.), crude dichlorodimethyl ether (100 g.), and fuming sulphuric acid (250 g., containing 20% of SO_3) were mixed, giving a homogeneous solution with heat evolution. This solution was heated on a water-bath for 3—5 minutes (further heating, which leads to considerable evolution of hydrogen chloride, must be avoided) and then set aside overnight. The solution was poured on ice, giving an oil which readily solidified. The crystals, when collected, washed with water and recrystallised from methyl alcohol or from light petroleum (b. p. 60—80°), gave the required *dichloride* as colourless crystals, m. p. 77° (Found : C, 46·5; H, 3·7; N, 5·7. $C_9H_9O_2NCl_2$ requires C, 46·15; H, 3·9; N, 6·0%); average yield, 41 g.

Synthesis of 5-Nitro-2-2′-bromoethylbenzyl Bromide.—(i) *2-p-Nitrophenylethyl bromide.* This was prepared by nitration of 2-phenylethyl bromide as Foreman and McElvain (*J. Amer. Chem. Soc.*, 1940, **62**, 1436) describe.

(ii) *s-Dibromodimethyl ether.* This preparation was based essentially on the method of Tischtschenko and Rabcevitsch-Zubkovski (*J. Russ. Phys. Chem. Soc.*, 1914, **46**, 705). Bromine (435 g.) was added slowly during 4 hours to water (28 c.c.), to which a mixture of paraformaldehyde (150 g.) and red phosphorus (34 g.) was also added at a comparable rate, the reaction mixture being water-cooled meanwhile. The final product was set aside for 20 hours, and the heavy crude ether layer was then separated, saturated with hydrogen bromide, and dried (P_2O_5) for 1 day. Distillation gave the ether as a fraction of b. p. 146—159°, sufficiently pure for the following bromomethylation stage; yield, 320 g.

(iii) *5-Nitro-2-2′-bromethylbenzyl bromide.* 2-*p*-Nitrophenylethyl bromide (75 g.), dibromodimethyl ether (225 g.), and fuming sulphuric acid (300 g., containing 20% of SO_3) were mixed, giving a homogeneous solution with heat evolution. This mixture was set aside for 48 hours and then poured on ice, a heavy reddish oil separating. The aqueous acid layer was decanted, and water was added to the reddish oil, which, when vigorously stirred and kneaded, ultimately solidified. The product, when collected, washed with water, drained, and recrystallised from alcohol, gave the required *dibromide* as colourless crystals, m. p. 92·5° (Found : C, 33·4; H, 2·9; N, 4·4. $C_9H_9O_2NBr_2$ requires C, 33·4; H, 2·8; N, 4·3%); yield, 58 g.

7-Nitro-2-p-tolyl-1 : 2 : 3 : 4-tetrahydroisoquinoline (VII; R = C_6H_4Me).—(*a*) The dichloride (VI) (23·4 g.), *p*-toluidine (10·7 g., 1 mol.), anhydrous potassium carbonate (50 g.), and *n*-butyl alcohol (150 c.c.) were heated under reflux for 3 hours and then allowed to cool. The mixture was poured into water, and the orange solid which separated was collected, washed, and recrystallised from alcohol; the crude tetrahydroisoquinoline (16 g.; m. p. 92—95°) thus obtained, when twice recrystallised from *n*-hexane, gave orange needles, m. p. 96·5—98° (Found : C, 71·9; H, 6·0; N, 10·6. $C_{16}H_{16}O_2N_2$ requires C, 71·6; H, 6·0; N, 10·45%).

(*b*) The dibromide (VIII) (3 g.), *p*-toluidine (1 g., 1 mol.), potassium carbonate (4 g.), and alcohol (20 c.c.) were heated under reflux for 2·5 hours. The cold mixture was filtered, and the residue washed free from carbonate with water and then recrystallised from the filtrate with the addition of more alcohol. The tetrahydroisoquinoline thus obtained had m. p. 94—96°; yield, 1·75 g. (70%).

When an excess of alcoholic hydrogen chloride was added to a hot alcoholic solution of the above compound, the mixture immediately became colourless. Cooling and scratching ultimately caused the *hydrochloride* to separate in colourless crystals, melting at 194—195·5° to a red liquid which rapidly decomposed (Found : C, 62·5; H, 5·8. $C_{16}H_{16}O_2N_2$,HCl requires C, 63·0; H, 5·6%).

7-Amino-2-p-tolyltetrahydroisoquinoline.—The above nitro-base (9·6 g.) was suspended in alcohol (50 c.c.) containing platinum oxide (0·08 g.) and reduced by shaking at 50° with hydrogen at atmospheric pressure. When hydrogen absorption ceased, the solution was boiled, filtered, and cooled, the 7-*amino*-compound readily crystallising; a second crop (giving 6·75 g. in all) was obtained by concentration of the mother-liquor. Recrystallisation from light petroleum (b. p. 60—80°) (charcoal) gave the colourless amine, m. p. 87·5—88° (Found : C, 80·5; H, 7·9; N, 11·8. $C_{16}H_{18}N_2$ requires C, 80·6; H, 7·6; N, 11·8%). The following derivatives, prepared in the usual way, were all recrystallised from alcohol and obtained as colourless compounds : 7-*acetamido*-, m. p. 186—188° (Found : C, 77·0; H, 7·0; N, 10·2. $C_{18}H_{20}ON_2$ requires C, 77·1; H, 7·2; N, 10·0%), 7-*benzamido*-, m. p. 156—158° (Found : C, 81·0; H, 6·7; N, 8·5. $C_{23}H_{22}ON_2$ requires C, 80·65; H, 6·5; N, 8·2%), 7-*benzenesulphonamido*-derivative, m. p. 160—165° (Found : C, 69·6; H, 5·7; N, 7·4. $C_{22}H_{22}O_3N_2S$ requires C, 69·8; H, 6·0; N, 7·4%).

3 : 4-Dimethoxyaniline hydrochloride. This was prepared from pyrocatechol by standard methods (Ullmann, *Annalen*, 1903, **327**, 115; Moureu, *Bull. Soc. chim.*, 1896, **15**, 647; Smith and Haller, *J. Amer. Chem. Soc.*, 1934, **56**, 237).

7-Nitro-2-(3′ : 4′-dimethoxyphenyl)-1 : 2 : 3 : 4-tetrahydroisoquinoline [VII; R = $C_6H_3(OMe)_2$].—A mixture of the dichloride (VI) (27·8 g.), 3 : 4-dimethoxyaniline hydrochloride (22·6 g., 1 mol.), potassium carbonate (60 g.), and *n*-propyl alcohol (200 c.c.) was heated under reflux for 2 hours and then filtered whilst hot. The filtrate on cooling deposited the 7-*nitro*-derivative (12·8 g.); the undissolved residue from the reaction mixture was digested with cold water, and a second crop (7·4 g.) thus obtained : total yield, 53%. The united crops, when recrystallised from alcohol, gave the pure 7-*nitro*-derivative as red crystals, m. p. 120—120·5° (Found : C, 64·75; H, 5·9; N, 9·2. $C_{17}H_{18}O_4N_2$ requires C, 64·9; H, 5·8; N, 8·9%).

This compound, when catalytically reduced as described above, gave the 7-*amino*-derivative in colourless crystals from alcohol, m. p. 144—144·5° (Found : C, 71·65; H, 6·9; N, 9·5. $C_{17}H_{20}O_2N_2$ requires C, 71·8; H, 7·1; N, 9·9%). The 7-*acetamido*-derivative also formed colourless crystals, m. p. 153—154°, from alcohol (Found : C, 70·1; H, 7·2; N, 8·65. $C_{19}H_{22}O_3N_2$ requires C, 69·9; H, 6·8; N, 8·6%).

7-Nitro-2-n-butyl-1 : 2 : 3 : 4-tetrahydroisoquinoline Hydrochloride.—A solution of the dichloride (VI) (4·16 g.) and *n*-butylamine (3·9 g., 3 mols.) in alcohol (20 c.c.) was heated under reflux for 30 minutes and then poured into water. The red oily *iso*quinoline which separated was extracted with ether, the solution dried (Na_2SO_4) and filtered, and the ether then removed. The residual red oil was dissolved in chloroform, which was then treated with hydrogen chloride. The crude *hydrochloride* (3·75 g.) which

separated was recrystallised from alcohol, giving colourless crystals, m. p. 224—226° (decomp.) (Found : C, 57·8; H, 7·0; N, 10·5. $C_{13}H_{15}O_3N_3$,HCl requires C, 57·4; H, 7·05; N, 10·3%).

*7-Nitro-2-2′-diethylaminoethyl-*1 : 2 : 3 : 4-*tetrahydroisoquinoline Dihydrochloride.*—This was prepared as the above compound, using the dichloride (VI) (16·8 g.), 2-diethylaminoethylamine (25·2 g., 3 mols.) and alcohol (120 c.c.). The red oil after removal of the ether was dissolved in acetone and treated with an acetone solution of hydrogen chloride. The precipitated *dihydrochloride* (22·3 g.), on recrystallisation from alcohol, gave colourless crystals, m. p. 232° (decomp.) (Found : C, 51·2; H, 7·45; N, 11·7. $C_{15}H_{23}O_3N_3$,2HCl requires C, 51·4; H, 7·2; N, 12·0%).

Catalytic reduction of this salt in alcohol gave the 7-*amino*-derivative *dihydrochloride*, as colourless crystals, m. p. 221—223° (decomp.), from alcohol (Found : C, 56·1; H, 8·25; N, 12·8. $C_{15}H_{25}N_3$,2HCl requires C, 56·2; H, 8·5; N, 13·1%). The 7-*acetamido*-derivative *dihydrochloride* also formed colourless crystals, m. p. 243—244° (decomp.), from alcohol (Found : C, 56·2; H, 8·0; N, 11·4. $C_{17}H_{27}ON_3$,2HCl requires C, 56·3; H, 8·1; N, 11·6%).

*7-Nitro-*2-p-*chlorophenyl-*1 : 2 : 3 : 4-*tetrahydroisoquinoline* (VII; R = C_6H_4Cl).—A mixture of the dibromide (VIII) (12 g.), *p*-chloroaniline (7·2 g., 1 mol.), potassium carbonate, and alcohol (120 c.c.) was boiled under reflux for 2·5 hours and filtered whilst hot. The 7-*nitro*-compound separated as yellow crystals in the filtrate, and a further quantity was obtained by cold aqueous digestion of the residue from the initial filtration to remove potassium carbonate. The total product (6·8 g.) was recrystallised from alcohol, giving the pure yellow crystalline base, m. p. 130—131° (Found : C, 62·4; H, 4·8; N, 10·0. $C_{15}H_{13}O_2N_2Cl$ requires C, 62·4; H, 4·5; N, 9·7%). The *hydrochloride* was prepared precisely similarly to that of the 2-*p*-tolyl analogue; it formed colourless crystals, melting at 191—192° to a red liquid which rapidly decomposed (Found : C, 55·4; H, 4·6. $C_{15}H_{13}O_2N_2Cl$,HCl requires C, 55·4; H, 4·3%).

Catalytic reduction of this base was unsatisfactory; the base was therefore reduced using tin and hydrochloric acid in aqueous alcohol; the 7-*amino*-compound thus obtained formed colourless crystals, m. p. 107—108° (Found : C, 70·0; H, 6·0; N, 11·2. $C_{15}H_{15}N_2Cl$ requires C, 69·6; H, 5·85; N, 10·8%). The 7-*acetamido*-compound also separated as colourless crystals, m. p. 171—172°, from alcohol (Found : C, 68·2; H, 6·0; N, 9·4. $C_{17}H_{17}ON_2Cl$ requires C, 67·85; H, 5·7; N, 9·3%).

*7-Nitro-*2-p-*acetamidophenyl-*1 : 2 : 3 : 4-*tetrahydroisoquinoline* (VII; R = C_6H_4·NHAc).—Prepared as the 2-*p*-chlorophenyl derivative, using the dibromide (VIII) (9 g.), *p*-aminoacetanilide (4·2 g., 1 mol.), potassium carbonate (12 g.), and alcohol (100 c.c.), and recrystallised from alcohol, the 7-*nitro*-compound formed yellow crystals, m. p. 216° (decomp.) (Found : C, 65·6; H, 5·8; N, 13·9. $C_{17}H_{17}O_3N_3$ requires C, 65·5; H, 5·5; N, 13·5%).

Catalytic reduction in alcohol gave the 7-*amino*-compound, colourless crystals, m. p. 159—160°, from alcohol (Found : C, 72·7; H, 7·1; N, 14·9. $C_{17}H_{19}ON_3$ requires C, 72·5; H, 6·8; N, 14·9%).

Several attempts were made to hydrolyse the above 7-nitro- and 7-amino-compounds with acids and with alkalis, and so to obtain the corresponding 2-*p*-aminophenyl derivatives, either as the free bases or at salts, but pure stable samples of these derivatives were not isolated.

We are indebted to Mr. H. Zeitlin, M.S., for assistance in the preliminary stages of this investigation carried out in the University of Hawaii with one of us (F. G. M.). We also gratefully acknowledge a grant from the Department of Scientific and Industrial Research (M. H. B.).

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, February 12th,* 1949.]

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386. *The Preparation of 4-Amino-2-styrylquinoline and Some Related Compounds.*

By RICHARD ROYER.

Studies on the relation between chemical constitution and antibacterial action have entailed the synthesis of compounds of the type of 4-amino-2-styrylquinoline, *-2-4′-phenylbutadienylquinoline,* and *-2 : 6-distyrylpyridine.* Some improvements in the preparation of necessary intermediates are recorded. A process is described for removing an active methyl group from a pyridine-type nucleus bearing in addition an amino-group.

JENSCH (*Z. angew. Chem.*, 1937, **50**, 891) claimed that 4-amino-2-styrylquinoline displayed remarkable bactericidal properties. According to Eisleb (D.R.-P. 440,008; U.S.P. 1,967,356), this and analogous compounds may be prepared by amination of the 4-chloro-2-styrylquinolines produced by heating 4-chloroquinaldines with an aldehyde and zinc chloride. Endeavours to repeat this work led to tars from which only a poor yield of the desired product could be isolated. Accordingly, condensation of a 4-aminoquinaldine with an aldehyde in the presence of acetic anhydride and hydrolysis of the resultant 4-acetamido-2-styrylquinoline were investigated. In general, acetic anhydride was preferable to zinc chloride as condensing agent despite the fact that the additional step of hydrolysis was involved; *e.g.*, by use of zinc chloride, the yield of pure 4-amino-2-styrylquinoline was 45%, whereas the acetic anhydride method gave a yield of 77%; again, no useful product was obtained in the reaction of 4-aminoquinaldine with cinnamaldehyde in the presence of zinc chloride, whereas acetic anhydride led to a moderate

yield of *4-acetamido-2-4'-phenylbutadienylquinoline*. The compounds listed in Tables I and II, and 4-amino-2 : 6-distyrylpyridine, were synthesised by this general method.

4-Amino-2-p-nitrostyrylquinoline was not prepared by this method, as *4-acetamido-2-p-nitrostyrylquinoline* proved unexpectedly resistant to hydrolysis. However it was obtained pure in moderate yield by heating 4-aminoquinaldine, *p*-nitrobenzaldehyde, and zinc chloride. The general method failed with 4-aminoquinaldine and *p*-dimethylaminobenzaldehyde, but the use of zinc chloride resulted in a 46% yield of *4-amino-2-4'-dimethylaminostyrylquinoline*.

Schmidt (*Ber.*, 1905, **38**, 3715) prepared 6-nitro-2-styrylquinoline by heating 6-nitroquinaldine and benzaldehyde with zinc chloride, purification involving several recrystallisations from alcohol. The preparation has been improved by using acetic anhydride in place of zinc chloride, an 84% yield of pure substance being isolated directly from the reaction mixture. Reduction by stannous chloride gave 6-amino-2-styrylquinoline, m. p. 197°. This compound has recently been prepared by a similar method by Brown and Kon (*J.*, 1948, 2147) who recorded m. p. 198—199°.

4-Amino-2 : 6-dimethylpyridine was first prepared by Marckwald (*Ber.*, 1894, **27**, 1325) by pyrolysis of the corresponding 3 : 5-dicarboxylic acid, obtained by a lengthy synthesis from acetonedicarboxylic ester. Later, it was prepared by heating 2 : 6-dimethylpyridine with sodamide in toluene (Tschitschibabin, *Chem. Zentr.*, 1916, **1**, 1032). It has been found that the base is conveniently obtained by reaction of 4-chloro-2 : 6-dimethylpyridine with ammonia in boiling *p*-cresol (the use of phenol at 180° gave only 35%); 4-amino-2 : 6-dimethylpyridine melts at 192° (186°, *locc. cit.*), being very readily purified by crystallisation from benzene.

4-Amino-2 : 8-dimethylquinoline has been prepared by Hofmann degradation of *2 : 8-dimethylcinchoninamide*, readily obtained by heating 7-methylisatin with acetone and ammonia (cf. D.R.-P. 290,703). Application of this method to 5-chloroisatin proved unsatisfactory for preparative purposes, and *6-chloro-4-aminoquinaldine* was produced more readily by aminating 4 : 6-dichloroquinaldine in phenol.

The product of a quinoline synthesis frequently bears a 2-methyl group whose elimination may be desirable. The facile preparation of 4-acetamido-2-styrylquinolines from 4-aminoquinaldines suggests such a method for a quinoline nucleus which bears also a 4-amino-group. *E.g.*, *4-acetamido-2-styrylquinoline* was oxidised to *4-acetamidoquinaldinic acid* which afforded 4-aminoquinoline by hydrolysis and subsequent decarboxylation (yields are good). Alternatively, 4-acetamidoquinaldinic acid could be decarboxylated to 4-acetamidoquinoline in 89% yield. Endeavours to effect simultaneous hydrolysis and decarboxylation of 4-acetamidoquinaldinic acid were unsuccessful; 65% sulphuric acid at a bath-temperature of 210° left the carboxyl group in place, and stronger acid caused sulphonation (for another example of this series of reactions, see Albert, Brown, and Duewell, *J.*, 1948, 1284).

Experimental.

M. p.s are not corrected.

4-Acetamido-2-styryl- and *-2-4'-phenylbutadienyl-quinoline*.—The appropriate 4-aminoquinaldine, acetic anhydride (3 mols.), and benzaldehyde, cinnamaldehyde, or anisaldehyde (3 mols.) were heated for 3 hours in a bath at 155—160°. Excess of aldehyde was removed by steam-distillation; the remaining solid was collected, ground under methanol (2 parts), and crystallised from a suitable solvent. Yields and analytical data for *compounds* prepared in this manner are given in Table I. The substances form white or pale yellow crystals.

Table I.

4-Acetamidoquinolines.

Substituents.	M. p.	Solvent.	Yield, %.	Formula.	Found, %. C.	H.	N.	Required, %. C.	H.	N.
2-Styryl	199·5°	67% ethanol	91	$C_{19}H_{16}ON_2$	78·6	5·6	9·8	79·1	5·6	9·7
8-Methyl-2-styryl	230	ethanol	83	$C_{20}H_{18}ON_2$	78·9	6·0	9·3	79·4	6·0	9·3
6-Ethoxy-2-styryl	216	ethanol	85	$C_{21}H_{20}O_2N_2$	75·2	6·0	8·45	78·85	6·1	8·4
6-Chloro-2-styryl	241·5	chlorobenzene	81	$C_{19}H_{15}ON_2Cl$			8·7			8·7
2-4'-Phenylbutadienyl	196	ethanol	53	$C_{21}H_{18}ON_2$	79·7	5·8	8·9	80·2	5·8	8·9
6-Ethoxy-2-4'-phenylbutadienyl	188	ethanol	65	$C_{23}H_{22}O_2N_2$	76·4	6·2	7·9	77·0	6·2	7·8
2-4'-Methoxystyryl	228	acetone	62	$C_{20}H_{18}O_2N_2$	74·9	5·7	8·8	75·4	5·7	8·8

4-Amino-2-styryl- and *-2-4'-phenylbutadienyl-quinoline*.—The appropriate 4-acetamido-compound was heated under reflux for 4—5 hours with 6N-hydrochloric acid (5 mols.). Ethanol (5 parts) was

added to the hydrolysis mixture in the cases of 6-chloro-4-acetamido- and 4-acetamido-6-ethoxy-2-styrylquinoline and of 4-acetamido-6-ethoxy-2-4′-phenylbutadienylquinoline. After the mixture had been cooled, the hydrochloride was filtered off and warmed with dilute ammonium hydroxide to liberate the base, which was purified by crystallisation from a suitable solvent. Yields and analytical data are given in Table II. The *compounds* form yellow or buff-coloured crystals, readily soluble in N-acetic acid. The hydrochlorides are bright yellow and only sparingly soluble in cold water. The amines do not diazotise normally.

TABLE II.

4-Aminoquinolines.

Substituents.	M. p.	Solvent.	Yield, %.	Formula.	Found, %. C.	H.	N.	Required, %. C.	H.	N.
2-Styryl	173·5° [a]	60% ethanol	85	$C_{17}H_{14}N_2$	82·5	5·8	11·3	82·9	5·7	11·4
8-Methyl-2-styryl	201	ethanol	99	$C_{18}H_{16}N_2$	82·5	6·1	10·7	83·0	6·2	10·8
6-Ethoxy-2-styryl	211 [b]	60% ethanol	94	$C_{19}H_{18}ON_2$	78·0	6·2	9·7	78·6	6·25	9·65
6-Chloro-2-styryl	228	chlorobenzene	88	$C_{17}H_{13}N_2Cl$	72·4	4·6	10·1	72·7	4·7	10·0
2-4′-Phenylbutadienyl	170—176 [c]	67% ethanol	83	$C_{19}H_{16}N_2$	83·2	6·0	10·3	83·8	5·9	10·3
6-Ethoxy-2-4′-phenylbutadienyl	207 [d]	ethanol	83	$C_{21}H_{20}ON_2$	79·6	6·4	8·9	79·7	6·4	8·9
2-4′-Methoxystyryl	164—165	chlorobenzene	97	$C_{18}H_{16}ON_2$	77·5	5·8	10·1	78·2	5·8	10·15

[a] D.R.-P. 440,008 gives m. p. 173—175° (decomp.).
[b] D.R.-P. 440,008 gives m. p. 212°.
[c] This wide melting-range was not altered by crystallisation from chlorobenzene.
[d] U.S.P. 1,967,356 gives m. p. 185—187°.

4-Amino-2-4′-dimethylaminostyrylquinoline.—4-Aminoquinaldine (1·0 g.) and *p*-dimethylaminobenzaldehyde (2·9 g.) were heated with pulverised anhydrous zinc chloride (0·1 g.) for 2 hours in a bath at 180—185°. The mass was then heated under reflux for 10 minutes with N-hydrochloric acid (20 ml.), and the dihydrochloride of *4-amino-2-4′-dimethylaminostyrylquinoline* was precipitated by the addition of concentrated hydrochloric acid (20 ml.). This salt was suspended in boiling 50% ethanol (50 ml.), and 2·5N-sodium hydroxide was added until the colour changed through red to yellow. The resulting solution was poured into water (200 ml.), and the base collected and crystallised from toluene (16 parts), giving deep-yellow crystals, m. p. 186° (46%) (Found: C, 78·5; H, 6·7; N, 14·5. $C_{19}H_{19}N_3$ requires C, 78·8; H, 6·6; N, 14·5%). The dihydrochloride is white, and the monohydrochloride scarlet, 1 part of the latter dissolving in *ca.* 800 parts of boiling water. The base is readily soluble in N-acetic acid and does not diazotise normally.

4-Amino-2-4′-aminostyrylquinoline and 4-Amino-2-4′-nitrostyrylquinoline.—(*a*) 4-Aminoquinaldine (3·2 g.), *p*-nitrobenzaldehyde (3·3 g., 1·1 mols.), and acetic anhydride (20·3 g., 10 mols.) were heated for 1 hour in a bath at 155—160°. The pale yellow crystals which separated on cooling were washed with glacial acetic acid, water, *and* a little ethanol, leaving pure *4-acetamido-2-4′-nitrostyrylquinoline*, m. p. 257—258° (50%) (Found: C, 67·9; H, 4·6; N, 12·7. $C_{19}H_{15}O_3N_3$ requires C, 68·4; H, 4·5; N, 12·6%). A further amount of crude material was obtained by making the mother-liquor alkaline. Reduction by stannous chloride in concentrated hydrochloric acid gave *4-acetamido-2-4′-aminostyrylquinoline* as yellow crystals (from 200 parts of ethanol), m. p. 247° (91%) (Found: N, 13·7. $C_{19}H_{17}ON_3$ requires N, 13·9%). This compound (0·35 g.) and 6N-hydrochloric acid (1·8 ml.) were heated under reflux for 3—5 hours; after the mixture had been cooled, the solid was basified by ammonium hydroxide, and the amine purified by extraction with N-acetic acid and basification of the extract. *4-Amino-2-4′-aminostyrylquinoline*, thus obtained in 80% yield, formed deep-yellow crystals, m. p. 202·5°, from ethanol (15 parts) (Found: C, 77·7; H, 5·8; N, 16·1. $C_{17}H_{15}N_3$ requires C, 78·1; H, 5·8; N, 16·1%). The diazo-solution is bright yellow and couples (crimson) with alkaline β-naphthol. The dihydrochloride is flesh-coloured, and the monohydrochloride orange-red, being moderately soluble in cold water.

(*b*) 4-Aminoquinaldine (3·3 g.), *p*-nitrobenzaldehyde (6·9 g.), and pulverised anhydrous zinc chloride (0·5 g.) were heated in a bath at 170° for 10 minutes and then boiled under reflux for 30 minutes with N-hydrochloric acid (50 ml.). After the excess of *p*-nitrobenzaldehyde had been removed by steam-distillation, the residual solid was boiled with dilute ammonium hydroxide solution, and the *4-amino-2-4′-nitrostyrylquinoline* purified by crystallisation from acetone; deep yellow crystals, m. p. 249°; yield, 49% (Found: N, 14·3. $C_{17}H_{13}O_2N_3$ requires N, 14·4%). The base formed gels with dilute acetic and lactic acid. Reduction by stannous chloride in concentrated hydrochloric acid gave 4-amino-2-4′-aminostyrylquinoline (91%), identical with the compound produced by method (*a*).

6-Amino-2-styrylquinoline.—6-Nitroquinaldine (3·8 g.), benzaldehyde (6·4 g., 3 mols.), and acetic anhydride (12·2 g., 6 mols.) were heated under reflux for 4 hours in a bath at 165—170°. After the mixture had been cooled, the solution deposited yellow crystals which were washed with a little glacial acetic acid and then with water, and dried at 120°, affording pure 6-nitro-2-styrylquinoline, m. p. 192° (84%). Reduction by stannous chloride in concentrated hydrochloric acid gave 6-amino-2-styrylquinoline (94%) as buff-coloured crystals, m. p. 197°, from ethanol (50 parts) or chlorobenzene (6 parts) (Found: C, 82·4; H, 5·7; N, 11·4. Calc. for $C_{17}H_{14}N_2$: C, 82·9; H, 5·7; N, 11·4%). The compound forms a yellow diazo-solution which couples (crimson) with alkaline β-naphthol.

4-Amino-2 : 6-distyrylpyridine. 4-Amino-2 : 6-dimethylpyridine (1·4 g.), acetic anhydride (7·2 g.,

6 mols.), and benzaldehyde (7·6 g., 6 mols.) were heated in a bath at 175—180° for 10 hours; excess of benzaldehyde was removed by steam-distillation leaving a semi-solid mass which was washed with water and dried in a desiccator. The solid so obtained was heated under reflux for 2·5 hours with 6N-hydrochloric acid (9 ml.) and ethanol (5 ml.), and the resulting mixture poured into excess of ammonium hydroxide, boiled for 30 minutes, and cooled. The liquid was decanted and the tarry residue triturated with cold ethanol (5 ml.), giving a solid, m. p. 220—221° (32%). Crystallisation from ethanol (70 parts) gave 4-*amino*-2 : 6-*distyrylpyridine* as light brown crystals, m. p. 223·5° (Found : C, 84·1; H, 6·0; N, 9·3. $C_{21}H_{18}N_2$ requires C, 84·5; H, 6·1; N, 9·4%).

4-*Amino*-2 : 8-*dimethylquinoline*.—7-Methylisatin (12 g.), ammonium hydroxide (10%; 74 ml.), and acetone (6 ml.) were heated under reflux for 1 hour and then cooled; crystalline 2 : 8-*dimethylcinchoninamide* (82%) was collected; m. p. 218—220°. Repeated recrystallisation from ethanol gave cream-coloured crystals, m. p. 224° (Found : N, 13·9. $C_{12}H_{12}ON_2$ requires N, 14·0%). This amide (9 g.) was added to a solution of bromine (7·3 g.) in 10% potassium hydroxide (125 ml.) at 5°; the resulting solution was stirred for 45 minutes at 5°, treated with more 10% potassium hydroxide (72 ml.), and after 5 minutes heated to 60° for 20 minutes. After the mixture had cooled, the crude 4-amino-2 : 8-dimethylquinoline was collected and purified by crystallising the hydrochloride from the minimum quantity of water and regenerating the base with 5N-sodium hydroxide; yield, 3·4 g.; m. p. 134—135°. Crystallisation from benzene raised the m. p. to 137°, not altered by crystallisation from water (Backeberg, *J.*, 1938, 1083, recorded m. p. 141°) (Found : C, 76·2; H, 7·0; N, 16·15. Calc. for $C_{11}H_{12}N_2$: C, 76·7; H, 7·0; N, 16·3%).

6-*Chloro*-4-*aminoquinaldine*.—Crude 4 : 6-dichloroquinaldine was prepared from 6-chloro-4-hydroxyquinaldine by phosphorus oxychloride according to the general method of Albert and Gledhill (*J. Soc. Chem. Ind.*, 1945, **64**, 169T). This substance (5 g.) and dried phenol (40 g.) were heated in a bath at 175—180° while a steady stream of ammonia was passed through the solution for 3 hours. After removal of phenol by steam-distillation, the solution was poured into excess of 5N-sodium hydroxide yielding 6-*chloro*-4-*aminoquinaldine*, m. p. 186° (77% based on 6-chloro-4-hydroxyquinaldine). Crystallisation from benzene (20 parts) gave white crystals, m. p. 186° (Found : C, 61·85; H, 4·7; N, 14·4. $C_{10}H_9N_2Cl$ requires C, 62·3; H, 4·7; N, 14·5%).

4-*Amino*-2 : 6-*dimethylpyridine*. 4-Chloro-2 : 6-dimethylpyridine (3·65 g.) and dry *p*-cresol (18 g.) were heated in a bath at 205—210° while a steady stream of dry ammonia was passed through the solution for 5 hours. Working up as above and crystallisation from benzene gave pure 4-amino-2 : 6-dimethylpyridine, m. p. 192° (72%) (Found : C, 68·5; H, 8·2; N, 22·7. Calc. for $C_7H_{10}N_2$: C, 68·8; H, 8·3; N, 22·9%).

4-*Acetamidoquinaldinic Acid*.—4-Acetamido-2-styrylquinoline (4·6 g.) in pyridine (32 ml.) and water (6·5 ml.) was stirred vigorously while powdered potassium permanganate (6·7 g.) was added during 1 hour, the internal temperature being kept at 18—20°. Water (total of 20 ml.) was added from time to time to permit stirring, as the mixture became thick with inorganic matter. Stirring was continued for 30 minutes, then the mixture was made acid to Congo-paper with dilute sulphuric acid and decolorised by the addition of sodium hydrogen sulphite. The precipitated acid was collected, washed with ether, and extracted with 2N-sodium carbonate; concentrated hydrochloric acid was added to the extract, precipitating the required acid, m. p. 237° (decomp.) (82%). Crystallisation from water (600 parts) gave 4-*acetamidoquinaldinic acid* as cream-coloured crystals, m. p. 238° (decomp.) (Found : C, 59·9; H, 4·6; N, 11·8. $C_{12}H_{10}O_3N_2.\frac{1}{2}H_2O$ requires C, 60·2; H, 4·6; N, 11·7%).

4-*Aminoquinaldinic Acid*.—4-Acetamidoquinaldinic acid (0·67 g.) was added to water (1 ml.) and sulphuric acid (*d* 1·84; 1 ml.) and heated under reflux in a bath at 208—210° for 2·5 hours. The solution was poured into water (2 ml.), and ammonium hydroxide solution added. 4-Aminoquinaldinic acid separated as light-brown crystals, m. p. 281—282° (decomp.) (68%) [cf. Bergstrom, *J. Org. Chem.*, 1938, **3**, 233, who recorded m. p. *ca.* 280·5—281° (decomp.)].

4-*Aminoquinoline*.—4-Aminoquinaldinic acid (0·37 g.) was heated in liquid paraffin (2·5 ml.) at 280—290° for 5 minutes. After cooling, the mixture was diluted with light petroleum (5 ml.), giving 4-aminoquinoline, 0·23 g., m. p. 152—153° after crystallisation from benzene. The m. p. was not depressed on admixture with an authentic specimen of anhydrous 4-aminoquinoline (m. p. 154°).

4-*Acetamidoquinoline*.—Liquid paraffin (10 ml.) was heated to 290° and stirred while 4-acetamidoquinaldinic acid (2 g.) was added during 5 minutes; after a further 5 minutes the mixture was cooled and diluted with light petroleum (5 ml.), giving 4-acetamidoquinoline (1·44 g.), m. p. 174—175° after crystallisation from water (cf. 176° recorded by Claus, *J. pr. Chem.*, 1897, **56**, 190).

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387. *Arylazotriarylmethanes and Tetra-arylsuccinic Dinitriles as Catalysts in Addition Polymerisation.*

By D. H. Hey and G. S. Misra.

Experiments are described on the polymerisation of styrene in which *p*-chloro- and *p*-bromo-phenylazotriphenylmethane, phenylazotri-*p*-methoxyphenylmethane and tetra-*p*-methoxyphenylsuccinic dinitrile are used as catalysts. For the substituted phenylazotriphenylmethanes there is evidence that both the aryl and the triarylmethyl radicals are incorporated in the polymer. The radicals derived from the substituted tetraphenylsuccinic dinitrile also become incorporated in the polymer.

Although the fundamental principles of the free-radical theory of addition polymerisation, which is supported by both chemical and kinetic evidence, are now firmly established, there remains a number of points on which further information is desirable. The present communication describes the results of experimental work designed to make a further contribution to the subject from the chemical standpoint. Investigations carried out by one of us fifteen years ago (Grieve and Hey, *J.*, 1934, 1797; Hey, *J.*, 1934, 1966 and subsequent papers) revealed the possibility of the occurrence of free radicals as transient intermediates in a number of organic reactions in solution and thus indicated the types of compound which might be active as catalysts for the initiation of addition polymerisation. The function of benzoyl peroxide in this respect was suggested by Hey and Waters (*Chem. Reviews*, 1937, **21**, 201), and the subsequent identification of fragments of the catalyst in the polymer molecule confirmed the hypothesis. By the use of *p*-bromobenzoyl peroxide, *p*-methoxybenzoyl peroxide, and chloroacetyl peroxide, polymers were obtained from styrene and methyl methacrylate which contained bromine, methoxyl, and chlorine, respectively (Price, Kell, and Krebs, *J. Amer. Chem. Soc.*, 1942, **64**, 1103). Similar results were later reported with 3 : 4 : 5-tribromobenzoyl peroxide (Price and Tate, *ibid.*, 1943, **65**, 517) and with *m*-bromobenzoyl peroxide (Pfann, Salley, and Mark, *ibid.*, 1944, **66**, 983). In like manner by the use of *p*-bromobenzenediazo hydroxide (Price and Durham, *ibid.*, 1942, **64**, 2508) and of substituted nitrosoacetanilides (Blomquist, Johnson, and Sykes, *ibid.*, 1943, **65**, 2446), polymers were again obtained in the molecules of which fragments of the catalyst were incorporated.

When a catalyst is employed which can be considered to give rise in solution to two different free radicals it would be reasonable to suppose that the more reactive radicals would play the predominant role in the initiation of the polymerisation process. The peroxides of organic acids can be regarded as sources of two types of radical because, provided that the temperature is not high, the peroxide can give both a hydrocarbon radical and an acid radical, thus :

$$(R{\cdot}CO_2)_2 \longrightarrow R{\cdot} + R{\cdot}CO{\cdot}O{\cdot} + CO_2$$

In agreement with this view Bartlett and Cohen (*ibid.*, 1943, **65**, 543) have shown that, when styrene is polymerised in the presence of *p*-bromobenzoyl peroxide, the polystyrene contains both *p*-bromophenyl and *p*-bromobenzoyloxy-groups. The groups are not, however, found in equal amounts and a differential activity is revealed since some 64% of the bromine in the polymer is present as *p*-bromobenzoyloxy- and some 36% as *p*-bromophenyl groups. The proportions in which the two different end groups are found depend upon the experimental conditions used. Similar results were recorded for the polymerisation of allyl acetate with *p*-chlorobenzoyl peroxide (Bartlett and Altschul, *ibid.*, 1945, **67**, 812). These results may be due in part to a step-wise decomposition of the catalyst, *e.g.*,

$$(R{\cdot}CO_2)_2 \longrightarrow 2R{\cdot}CO{\cdot}O{\cdot}$$
$$2R{\cdot}CO{\cdot}O{\cdot} \longrightarrow R{\cdot}CO{\cdot}O{\cdot} + R{\cdot} + CO_2$$

and the possibility of similar considerations arising with catalysts which provide free radicals with liberation of nitrogen must not be overlooked. An even greater differential effect was revealed in the work of Blomquist, Johnson, and Sykes (*loc. cit.*), who used as catalysts a series of substituted nitrosoacylanilides, which can also give two types of radical, thus :

$$Ar{\cdot}N(NO){\cdot}COR \rightleftharpoons Ar{\cdot}N{:}N{\cdot}O{\cdot}COR \longrightarrow Ar{\cdot} + R{\cdot}CO{\cdot}O{\cdot} + N_2$$

The results obtained indicated that only the active free aryl radical, Ar·, becomes incorporated in the polymer molecule and that the free acyloxy-radical, R·CO·O·, appears not to be involved. The contrast with the behaviour of the peroxides, which also yield an aryl and an acyloxy-radical, was unexpected, but may be attributed in part to the fact that the experiments with

the peroxides made use mainly of aromatic acyloxy-radicals, whereas, in the experiments with the nitrosoacylarylamines, only aliphatic acyloxy-radicals were used. A recent re-examination of the use of nitrosoacylarylamines containing aromatic acyloxy-groups (Hey and Misra, *Faraday Soc. Discussion*, 1947, **2**, 279) provided some indication that both aryl and acyloxy-groups were incoporated into the polymer molecules, although under these conditions the aryl radicals still appeared to be the more active.

In order to obtain further information on the differential incorporation of catalyst fragments in polymer molecules attention has now been directed to the use of substituted phenylazotriphenylmethanes, which on heating can give two free radicals of markedly different stability, thus:

$$R{\cdot}N{:}N{\cdot}CR'_3 \longrightarrow R\cdot + R'_3C\cdot + N_2$$

The use of the unsubstituted phenylazotriphenylmethane as a catalyst in the polymerisation of styrene was first reported by Schulz (*Naturwiss.*, 1939, **27**, 659), but there appear to be no records of the use of substituted phenylazotriphenylmethanes and in the absence of a substituent atom or group, which can be qualitatively identified, the incorporation of either or both radicals into the polymer cannot be readily observed. Experiments have now been carried out with phenylazotriphenylmethanes as catalysts for the polymerisation of styrene and methyl methacrylate in which either (*a*) the single phenyl group carries a chlorine or bromine atom at the *para*-position or (*b*) the triphenylmethyl group is replaced by the tri-*p*-methoxyphenylmethyl group. Analysis of the purified polymers for either halogen or methoxyl showed that both types of radical can become incorporated into the polymer molecules, and it is possible that, whereas the more active aryl radicals play the dominant role in initiating the polymerisation process, the much more stable triarylmethyl radicals act as retarders and cause chain termination. It is known that free radicals of the triarylmethyl type are able to add to certain ethylenic systems (Conant and Scherp, *J. Amer. Chem. Soc.*, 1931, **53**, 1941; Conant and Chow, *ibid.*, 1933, **55**, 3475; Marvel, Dec, and Corner, *ibid.*, 1945, **67**, 1855), and, with styrene, triphenylmethyl gives rise to a 1 : 2-adduct. Mayo and Gregg (*ibid.*, 1948, **70**, 1284) have suggested that with a radical of the stability associated with triphenylmethyl almost as many chains may be stopped as started, and that its function as catalyst or inhibitor is not clear-cut. On the other hand, Schulz (*loc. cit.*) considers that both the aryl and triarylmethyl radicals act as initiators and has suggested that in the polymerisation of styrene with phenylazotriphenylmethane the termination of the chain reaction is less likely to arise from dimerisation and that with relatively high concentrations of the catalyst the termination process may be due to combination with a free radical from the catalyst. It may be noted that experiments designed to place *different* labelled end-groups at either end of polystyrene molecules have already been reported by Price and Read (*J. Polymer Res.*, 1946, **1**, 44).

The use of tetraphenylsuccinic dinitrile as a catalyst for the polymerisation of styrene and methyl methacrylate was reported by Schulz and Wittig (*Naturwiss.*, 1939, **27**, 387; *Kunstoffe*, 1943, **33**, 224). Its function as a catalyst presumably results from its dissociation into two diphenylcyanomethyl radicals, thus:

$$\left.\begin{matrix}Ph_2C{\cdot}CN\\ Ph_2C{\cdot}CN\end{matrix}\right\} \rightleftharpoons 2Ph_2C{\cdot}CN$$

The incorporation of fragments of this catalyst into polymers prepared from styrene is shown by the presence of nitrogen, but in order to confirm the presence of the free-radical catalyst experiments have now been carried out with tetra-*p*-methoxyphenylsuccinic dinitrile and styrene using solutions in dioxan in order to favour the formation of polymers of low molecular weight. The use of this substituted tetraphenylsuccinic dinitrile has the further advantage that, according to Löwenbein and Gagarin (*Ber.*, 1925, **58**, 2643), tetra-*p*-methoxyphenylsuccinic dinitrile dissociates into two di-*p*-methoxyphenylcyanomethyl radicals at temperatures between 60° and 80° with the production of a rose-red colour, whereas a temperature of 140° is required for the production of a similar colour with tetraphenylsuccinic dinitrile (cf. Wittig *et al.*, *Annalen*, 1934, **513**, 26; *Ber.*, 1936, **69**, 790). In spite of these observations it was found that at temperatures below 97° the effect of any di-*p*-methoxyphenylcyanomethyl radicals so formed was negligible, and that the resulting polymers, when purified by precipitation from ethyl acetate solution, did not contain methoxyl groups. In polymerisation experiments carried out at 97—98° the rose-red colour due to the free radicals disappeared within fifteen minutes, but, if the polymerisation was stopped at this stage, again no methoxyl groups were found in the purified polymers and a considerable quantity of the adduct of styrene with the dinitrile, which

was removed by its comparative insolubility in cold ethyl acetate, was isolated. If, however heating was continued for at least a further fifteen minutes after the disappearance of the colour, the polymers thus formed were found to contain fragments of the catalyst. With high concentrations of the catalyst the main product consisted of the adduct. Schulz and Wittig (*loc. cit.*) had reported the formation of a similar adduct in their experiments with tetraphenylsuccinic dinitrile. The polymerisation of styrene with a chlorinated tetraphenylsuccinic dinitrile has been studied by Raff, but no experimental details are available (see Abere, Goldfinger, Mark, and Naidus, *Ann. N.Y. Acad. Sci.*, 1943, **44**, 293).

Experimental.

Preparation of Materials.

Styrene and Methyl Methacrylate.—The sample of styrene was left in contact with solid potassium hydroxide to remove quinol and, after decantation, distilled under reduced pressure, the middle fraction alone being used. The methyl methacrylate was purified similarly.

Phenylazotriphenylmethane, p-Chlorophenylazotriphenylmethane, and Phenylazotri-p-methoxyphenylmethane.—These compounds were prepared by the method of Wieland, Popper, and Seefried (*Ber.*, 1922, **55**, 1816). Phenyl- and *p*-chlorophenyl-hydrazotriphenylmethane were oxidised by potassium ferricyanide as described by Wieland, vom Hove, and Börner (*Annalen*, 1926, **446**, 31), but for the oxidation of phenylhydrazotri-*p*-methoxyphenylmethane silver oxide was used.

p-*Bromophenylazotriphenylmethane.*—A mixture of triphenylchloromethane (5 g.) and *p*-bromophenylhydrazine (7·62 g.) in absolute ether (100 c.c.) was boiled under reflux for 4 hours. After the mixture had been kept overnight the precipitated *p*-bromophenylhydrazine hydrochloride was filtered off and the filtrate, made up to 250 c.c. with ether, was oxidised with an aqueous alkaline solution of potassium ferricyanide (26 g. in 80 c.c.). The ethereal layer was separated, washed several times with water, and finally dried ($CaCl_2$). After removal of the ether under reduced pressure, p-*bromophenylazotriphenylmethane* (4·8 g.) was obtained, which after crystallisation from benzene–alcohol melted at 110° (Found: C, 70·0; H, 4·6. $C_{25}H_{19}N_2Br$ requires C, 70·25; H, 4·5%).

Tetraphenylsuccinic Dinitrile.—Diphenylacetonitrile, prepared by the method of Wittig and Petri (*Annalen*, 1934, **513**, 39) from diphenylchoromethane, was converted into tetraphenylsuccinic dinitrile by the action of iodine in sodium ethoxide solution (Auwers and Meyer, *Ber.*, 1889, **22**, 1228).

*Tetra-*p*-methoxyphenylsuccinic Dinitrile.*—Di-*p*-methoxyphenylacetonitrile was prepared from *p*-methoxymandelonitrile and an excess of anisole in presence of concentrated sulphuric acid (Bistrzycki, Paulus, and Perrin, *Ber.*, 1911, **44**, 2606). The action of alkaline potassium ferricyanide on di-*p*-methoxyphenylacetonitrile afforded tetra-*p*-methoxyphenylsuccinic dinitrile in 57% yield. The substance melts indefinitely at 220° (with red coloration) (cf. Löwenbein and Gagarin, *loc. cit.*).

*Tetra-*p*-methoxyphenylsuccinic Dinitrile–Styrene Adduct.*—Tetra-*p*-methoxyphenylsuccinic dinitrile (1 g.) was aded to boiling styrene (5 c.c.), and the mixture heated under reflux for a few minutes until the rose colour which appeared at the beginning faded to a straw-yellow. The mixture was cooled and the precipitated solid was crystallised from ethyl acetate. The *adduct* (0·56 g.) separated in hexagonal plates, m. p. 213—214° (Found: C, 78·6; H, 5·95. $C_{40}H_{36}O_4N_2$ requires C, 78·9; H, 6·0%).

Polymerisation Studies.

For the determination of the molecular weight of purified samples of polystyrene, viscosities were measured with an Ostwald viscometer, and the revised equation of Kemp and Peters (*Ind. Eng. Chem.*, 1942, **34**, 1097), *viz.*, $M = \log \eta_r \times K_{cm.}/C$, where $K_{cm.} = 0{\cdot}45 \times 10^4$ for polystyrene in benzene and η_r is the relative viscosity, has been used. To calculate the molecular weights of samples of polymerised methyl methacrylate, the original Staudinger equation, $M = \eta_{sp.}/CK_m$, where $K_m = 1{\cdot}7 \times 10^{-4}$ for methyl methacrylate in benzene and $\eta_{sp.}$ is the specific viscosity, was used. Typical approximate formulæ are ascribed, where possible, to the polymers formed based on the observed molecular weight ±500.

(1) A mixture of styrene (9·07 g.) and phenylazotriphenylmethane (1 g.) was heated on the boiling water-bath for 18 hours. The crude polystyrene was dissolved in dioxan and precipitated by pouring into methyl alcohol. The polymer (8 g.) was purified by three such reprecipitations (Found: C, 89·8; H, 7·4%; *M*, 23,560).

(2) A mixture of styrene (18·15 g.), *p*-bromophenylazotriphenylmethane (3 g.), and benzene (80 c.c.) was heated under reflux on a water-bath for 5 hours. The crude polystyrene was purified as described above and weighed 0·50 g. after one purification [Found: C, 88·8; H, 7·3; Br, 2·5%; *M*, 12,810. $C_6H_4Br{\cdot}(C_8H_8)_{120}{\cdot}C_6H_4Br$ requires C, 91·2; H, 7·6; Br, 1·25%; *M*, 12,792].

(3) A mixture of styrene (5·21 g.) and *p*-bromophenylazotriphenylmethane (0·62 g.) was heated in a sealed ampoule at 78° for 48 hours. The reaction was then brought to an abrupt end by chilling The crude polymer (4·5 g.), obtained by dissolving the reaction mixture in dioxan and pouring this into an excess of methyl alcohol, was purified three times in this way. The purified polymer weighed 3·75 g. [Found: C, 90·4; H, 7·4; Br, 1·8%; *M*, 15,080. $C_6H_4Br{\cdot}(C_8H_8)_{140}{\cdot}C_6H_4Br$ requires C, 91·4; H, 7·6; Br, 1·1%; *M*, 14,872].

(4) A mixture of styrene (4·54 g.), *p*-chlorophenylazotriphenylmethane (2 g.), and dioxan (25 c.c.) was boiled under reflux for 5 hours under nitrogen. The crude polymer (0·5 g.) was purified three times as above by reprecipitation [Found: C, 90·6; H, 7·3; Cl, 1·5%; *M*, 2,980. $C_6H_4Cl{\cdot}(C_8H_8)_{25}{\cdot}C(C_6H_5)_3$ requires C, 91·4; H, 7·4; Cl, 1·2%; *M*, 3,058. $C_6H_4Cl{\cdot}(C_8H_8)_{25}{\cdot}C_6H_5$ requires C, 91·2; H, 7·5; Cl, 1·3%; *M*, 2,816].

(5) A mixture of styrene (5·44 g.) and *p*-chlorophenylazotriphenylmethane (1 g.) was heated in a sealed ampoule at 65° for 48 hours. The crude polymer (1·2 g.), obtained by dissolving the reaction mixture in dioxan and pouring the solution into an excess of methyl alcohol, was purified three times by

reprecipitation [Found : C, 91·3; H, 7·5; Cl, 0·9%; *M*, 4,700. $C_6H_4Cl\cdot(C_8H_8)_{42}\cdot C(C_6H_5)_3$ requires C, 91·7; H, 7·5; Cl, 0·75%; *M*, 4,723. $C_6H_4Cl\cdot(C_8H_8)_{42}\cdot C_8H_9$ requires C, 91·7; H, 7·6; Cl, 0·8%; *M*, 4,688].

(6) A mixture of styrene (4·91 g.) and *p*-chlorophenylazotriphenylmethane (1 g.) was heated in a sealed ampoule at 85° for 22 hours. The polymer, isolated and purified as in the previous case, weighed 2·2 g. [Found : C, 9·18; H, 7·9; Cl, 0·9%; *M*, 8,240. $C_6H_4Cl\cdot(C_8H_8)_{76}\cdot C(C_6H_5)_3$ requires C, 92·0; H, 7·6; Cl, 0·4%; *M*, 8,260. $C_6H_4Cl\cdot(C_8H_8)_{78}\cdot C_6H_4Cl$ requires C, 91·6; H, 7·6; Cl, 0·85%; *M*, 8,336].

(7) A mixture of styrene (5·44 g.) and *p*-chlorophenylazotriphenylmethane (0·996 g.) was heated in a sealed ampoule at 95° for 22 hours. The polymer, isolated and purified as in experiment (5), weighed 2·5 g. [Found : C, 90·55; H, 8·7; Cl, 0·3%; *M*, 17,740. $C_6H_4Cl\cdot(C_8H_8)_{169}\cdot C_8H_9$ requires C, 92·1; H, 7·7; Cl, 0·2%; *M*, 17,792].

(8) A mixture of styrene (4·54 g.) and *p*-chlorophenylazotriphenylmethane (0·993 g.) was sealed in an ampoule and maintained at 100° for 18 hours. The crude polymer was purified three times in the usual way and weighed 2·5 g. [Found : C, 91·2; H, 7·7; Cl, 0·6%; *M*, 16,480. $C_6H_4Cl\cdot(C_8H_8)_{156}\cdot C_6H_4Cl$ requires C, 91·9; H, 7·6; Cl, 0·4%; *M*, 16,447].

(9) A mixture of *p*-chlorophenylazotriphenylmethane (1 g.), styrene (4·537 g.), and dioxan (10 c.c.) was heated in a sealed ampoule at 80° for 5 hours. The contents were poured into methyl alcohol, but no precipitate was formed. On addition of water, globules of an oily liquid separated. The mixture was shaken with ether and cooled. The ethereal layer was then poured into an excess of ice-cold methyl alcohol. A powdery polymer separated which was again purified in the same way (Found : Cl, 1·0%).

(10) A mixture of phenylazotri-*p*-methoxyphenylmethane (0·50 g.), styrene (9·074 g.), and dioxan (10 c.c.) was boiled under reflux for 3 hours under nitrogen. The crude polymer, obtained by pouring the dioxan solution into methyl alcohol, was purified three times in the usual way and afforded 1 g. of pure polystyrene [Found : C, 92·1; H, 7·9; OMe, 0·7%; *M*, 11,770. $C_6H_5\cdot(C_8H_8)_{110}\cdot C(C_6H_4\cdot OCH_3)_3$ requires C, 91·9; H, 7·6; OMe, 0·8%; *M*, 11,850].

(11) A mixture of phenylazotri-*p*-methoxyphenylmethane (0·50 g.) and styrene (4·537 g.) was maintained at 100° under nitrogen for 2 hours. The crude polystyrene (2·3 g.) was purified several times by reprecipitation [Found : C, 91·4; H, 7·7; OMe, 0%; *M*, 13,520. $C_6H_5\cdot(C_8H_8)_{128}\cdot C_6H_5$ requires C, 92·3; H, 7·7; *M*, 13,466].

(12) A mixture of phenylazotri-*p*-methoxyphenylmethane (0·50 g.), styrene (4·54 g.), and dioxan (10 c.c.) was heated in a sealed ampoule at 80° for 6 hours. The mixture was poured into an excess of methyl alcohol, and the crude polymer (0·50 g.) which separated was purified three times by reprecipitation [Found : C, 89·7; H, 7·3; OMe, 1·6%; *M*, 12,900. $C_6H_5\cdot(C_8H_8)_{120}\cdot C(C_6H_4\cdot OCH_3)_3$ requires C, 92·0; H, 7·6; OMe, 0·7%; *M*, 12,890. $(CH_3O\cdot C_6H_4)_3C\cdot(C_8H_8)_{114}\cdot C(C_6H_4\cdot OCH_3)_3$ requires C, 91·6; H, 7·6; OMe, 1·5%; *M*, 12,730].

(13) A mixture of *p*-chlorophenylazotriphenylmethane (2·001 g.) and methyl methacrylate (10·681 g.) was sealed in an ampoule and heated at 65° for 24 hours. The crude polymer (2·5 g.), obtained by dissolving the reaction mixture in dioxan and pouring into an excess of methyl alcohol, was purified three times by reprecipitation and weighed 1·5 g. [Found : C, 59·4; H, 7·6; Cl, 0·8%; *M*, 7,303. $C_6H_4Cl\cdot(C_5H_8O_2)_{71}\cdot C_5H_8O_2$ requires C, 60·1; H, 7·9; Cl, 0·5%; *M*, 7,312].

(14) A mixture of tetraphenylsuccinic dinitrile (1 g.), styrene (4 c.c.), and dioxan (20 c.c.) was heated under reflux for 3 hours under nitrogen. The crude polystyrene (2·5 g.), obtained by pouring the reaction mixture into an excess of methyl alcohol, was dissolved in ethyl acetate. A small portion of the solid which did not dissolve was found to be the adduct of styrene and the dinitrile, m. p. 224°. The polystyrene was then obtained by pouring the filtrate into methyl alcohol. It was purified three times in this way [Found : C, 91·3; H, 7·3; N, 1·8%; *M*, 9,888. $(C_6H_5)_2(CN)C\cdot(C_8H_8)_{90}\cdot C(CN)(C_6H_5)_2$ requires C, 92·1; H, 7·6; N, 0·6%; *M*, 9,744].

(15) A mixture of tetra-*p*-methoxyphenylsuccinic dinitrile (0·50 g.), styrene (4·54 g.), and dioxan (15 c.c.) was heated in a sealed ampoule at 80° for 6 hours. The crude polymer, obtained by pouring the dioxan mixture into methyl alcohol, was dissolved in ethyl acetate. A small portion of the solid remained undissolved and was identified as the adduct of styrene with the dinitrile, m. p. 212—214°. The polymer was precipitated on pouring the filtrate into methyl alcohol and was further purified by two more precipitations (Found : C, 90·7; H, 7·6%; OMe, 0; *M*, 17,420).

(16) A mixture of tetra-*p*-methoxyphenylsuccinic dinitrile (0·50 g.), styrene (4.54 g.), and dioxan (10 c.c.) was heated in a sealed ampoule at 80° for 6 hours. The crude polymer was purified three times by dissolving it in ethyl acetate and pouring into an excess of ice-cold methyl alcohol (Found : C, 91·2; H, 7·8%; OMe, 0; *M*, 20,250).

(17) A mixture of tetra-*p*-methoxyphenylsuccinic dinitrile (0·50 g.), styrene (13·61 g.), and dioxan (60 c.c.), was heated under reflux under nitrogen for 1 hour The rose-red colour disappeared in about 10 minutes. The crude polymer was purified as in the previous examples [Found : C, 91·4; H, 7·4; OMe, 2·1%; *M*, 8,702. $(CH_3O\cdot C_6H_4)_2(CN)C\cdot(C_8H_8)_{74}\cdot C(CN)(C_6H_4\cdot OCH_3)_2$ requires C, 91·3; H, 7·6; OMe, 1·5%; *M*, 8,100].

(18) A mixture of tetra-*p*-methoxyphenylsuccinic dinitrile (1·00 g.), styrene (9·074 g.), and dioxan (15 c.c.) was heated at 90° for 2 hours. When the mixture was poured into ice-cold methyl alcohol, the crude polymer (0·70 g.) separated. It was purified twice by precipitation from ethyl acetate (Found : C, 90·9; H, 7·5%; OMe, 0; *M*, 15,720). From the first filtrate some adduct was obtained.

(19) A mixture of tetra-*p*-methoxyphenylsuccinic dinitrile (0·50 g.), styrene (9·074 g.), and dioxan (20 c.c.) was heated at 95° for 2 hours. The crude polymer (0·70 g.), obtained by pouring the mixture into ice-cold methyl alcohol, was purified twice by precipitation from ethyl acetate (Found : C, 91·5; H 7·65%; OMe, 0; *M*, 18,890). As before, some adduct was obtained.

(20) A mixture of tetra-*p*-methoxyphenylsuccinic dinitrile (1 g.), styrene (9·074 g.), and dioxan (50 c.c.) was heated under reflux under nitrogen for ½ hour. The bulk of the dioxan was evaporated under reduced pressure, and the crude polymer (2 g.) was purified three times by precipitation from ethyl acetate [Found : C, 90·05; H, 7·6; OMe, 1·6%; *M*, 5,274.
$(CH_3O\cdot C_6H_4)_2(CN)C\cdot(C_8H_8)_{46}\cdot C(CN)(C_6H_4\cdot OCH_3)_2$ requires C, 90·8; H, 7·5; OMe, 2·35%; *M*, 5,288].

(21) A mixture of tetra-*p*-methoxyphenylsuccinic dinitrile (1·20 g.), styrene (9.074 g.), and dioxan (60 c.c.) was heated under reflux under nitrogen for 16 minutes. The reaction was stopped as soon as the pink colour disappeared. A small quantity of the crude polymer was obtained and purified as described above (Found : C, 86·9; H, 7·5%; OMe, 0; *M*, 8,017).

(22) A mixture of styrene (9·074 g.), dioxan (50 c.c.), and tetra-*p*-methoxyphenylsuccinic dinitrile (1 g.) was heated under reflux for 15 minutes under nitrogen. The crude polystyrene was purified as described above (Found : C, 90·6; H, 7·5%; OMe, 0).

(23) A mixture of styrene (9·074 g.) and dioxan (50 c.c.) was heated under reflux for 15 minutes under nitrogen. The crude product (0·70 g.), obtained by taking off the bulk of dioxan under reduced pressure and pouring the residue into methyl alcohol, was purified by precipitation from ethyl acetate (Found : *M*, 9,949).

(24) A mixture of styrene (9·074 g.), dioxan (50 c.c.), and tetra-*p*-methoxyphenylsuccinic dinitrile (1 g.) was heated under reflux under nitrogen for ¾ hour. The crude polymer (1·3 g.) was purified three times by precipitation from ethyl acetate [Found : C, 90·95; H, 7·6; OMe, 0·4%; *M*, 11,360. $(CH_3O{\cdot}C_6H_4)_2(CN)C{\cdot}(C_8H_8)_{105}{\cdot}C_8H_9$ requires C, 90·0; H, 7·7; OMe, 0·55%; *M*, 11,276].

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388. *The Photochemistry of Selenium. Part II. The Kinetics of the Oxidation of Hydrogen Selenide.*

By R. W. PITTMAN.

Kinetic measurements have been made on the photochemical oxidation of hydrogen selenide in the presence of liquid water and selenium. The reaction is shown to be of the first order with respect to oxygen and of half order with respect to hydrogen selenide, and the reaction rates to be dependent on only some small fractional power of the light intensity. A suggestion is made regarding the mechanism of this reaction.

A QUALITATIVE description of the reaction between oxygen and hydrogen selenide was given in Part I of this series (Ives and Pittman, *J.*, 1948, 766). It was shown that, for oxidation to occur, the presence of selenium and water were necessary and that reaction was promoted by light in the near ultra-violet and visible regions. This paper describes a quantitative investigation of the same system.

It is surprising, in view of the heterogeneity of the reaction system, that the kinetics have proved to be simple, and the results, which are self-consistent and reproducible, suggest a novel explanation of the reaction mechanism.

The apparatus used was similar to that described in Part I. The dependence of reaction rate on pressures of reactants was studied in a series of isolation experiments in which an attempt was made to measure instantaneous rates at arbitrary fixed pressures of one or other of the reactants. The procedure adopted was to admit oxygen and hydrogen selenide to the reaction bulb, which already contained water and a preformed film of selenium, to pressures in slight excess of those at which the rate was to be determined. This excess was so estimated that the required pressure conditions were attained after, say, 1½ hours of illumination. The reaction vessel was then alternately illuminated and darkened for periods of one hour until the desired pressure was adequately " bracketed." The total pressure within the vessel was measured at the beginning and end of each hour of illumination, and the observed pressure decrement was assumed to be approximately equal to the instantaneous rate corresponding to the mean pressures of reactants obtaining over that hour. These rates were then plotted against the products $P_{O_2}P_{H_2Se}^{\frac{1}{2}}$, P_{O_2} and P_{H_2Se} being respectively the mean pressures of oxygen and hydrogen selenide just mentioned. The instantaneous rate, under the desired conditions of pressure, was then obtained from this plot by interpolation. The rates given by this method for predetermined pressures of reactants are shown in Figs. 1 and 2 (and in Table I), in which reaction rate is plotted against the half-power of the pressure of hydrogen selenide at constant oxygen pressure and the first power of the pressure of oxygen at constant pressure of hydrogen selenide.

These results leave no doubt that the following rate equation may be written :

$$\mathrm{d}(P_{H_2Se})/\mathrm{d}t = k(P_{H_2Se})^{\frac{1}{2}} . (P_{O_2}) \quad . . . . . (1)$$

In a continuous reaction the rate may be defined by the equation :

$$\mathrm{d}x/\mathrm{d}t = k(a - x)^{\frac{1}{2}} . (b - \tfrac{1}{2}x) \quad . . . . . (2)$$

where a and b are the number of moles of hydrogen selenide and oxygen, respectively, initially

present in the reaction vessel, and x is the number of moles of hydrogen selenide oxidised in a time t. For the case in which oxygen is in excess, this gives on integration and substitution :

$$t = -\frac{4}{k2(P^{i}_{O_2} - \frac{1}{2}P^{i}_{H_2Se})}\tan^{-1}\frac{P_{H_2Se}}{2(P^{i}_{O_2} - \frac{1}{2}P_{H_2Se})}$$

where P^{i} refers to initial pressures and P to pressures at a time t. k can therefore be evaluated by plotting the variable part of this equation against time. This method was used in the preliminary

FIG. 1.

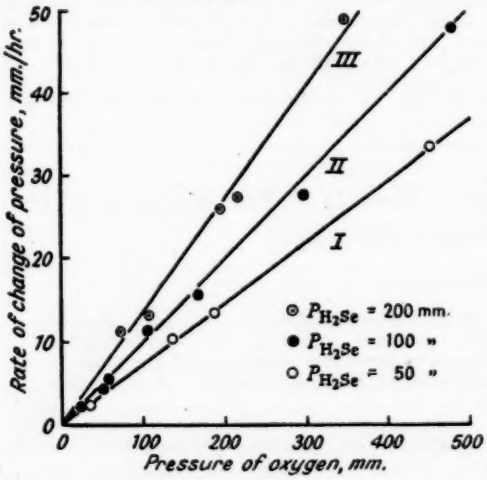


FIG. 2.

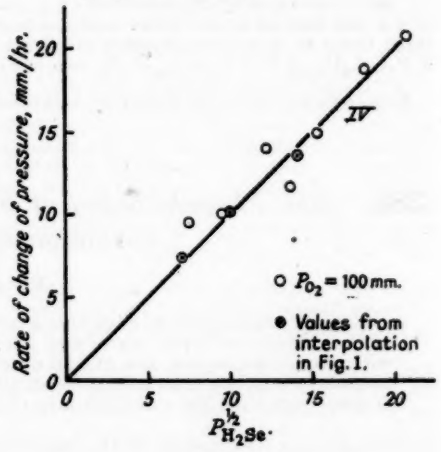


TABLE I.

Pressure of H_2Se = 50·0 mm. Fig. 1, Curve I.

P_{O_2}, mm.	35·0	135·2	187·2	450·0
dP/dt, mm./hr.	2·3	10·4	13·5	33·6

Slope Curve I = $m_1 = 7{\cdot}4 \times 10^{-2}$. $k = \frac{2}{3}m_1/50\dot{1} = 7{\cdot}0 \times 10^{-3}$.

Pressure of H_2Se = 100·0 mm. Fig. 1. Curve II.

P_{O_2}, mm.	22·5	50·6	57·5	59·7	105·0	160·7	296·3	474·3
dP/dt, mm./hr.	2·1	4·3	5·6	5·8	11·4	15·8	27·8	48·0

Slope Curve II = $m_2 = 10{\cdot}1 \times 10^{-2}$. $k = \frac{2}{3}m_2/100\dot{1} = 6{\cdot}8 \times 10^{-3}$.

Pressure of H_2Se = 200·0 mm. Fig. 1. Curve III.

P_{O_2}, mm.	73·0	108·0	193·3	214·8	346·9
dP/dt, mm./hr.	11·3	13·2	26·0	27·4	49·0

Slope Curve III = $m_3 = 13{\cdot}7 \times 10^{-2}$. $k = \frac{2}{3}m_3/200\dot{1} = 6{\cdot}4 \times 10^{-3}$.

Pressure of O_2 = 100·0 mm. Fig. 2. Curve IV.

P_{H_2Se}, mm.	431·3	333·0	238·3	147·3	185·0	90·0	57·3
dP/dt, mm./hr.	20·8	18·3	15·4	12·1	13·6	9·5	7·6

Slope Curve IV = $m_4 = 1{\cdot}0$. $k = \frac{2}{3}m_4/100 = 6{\cdot}7 \times 10^{-3}$.

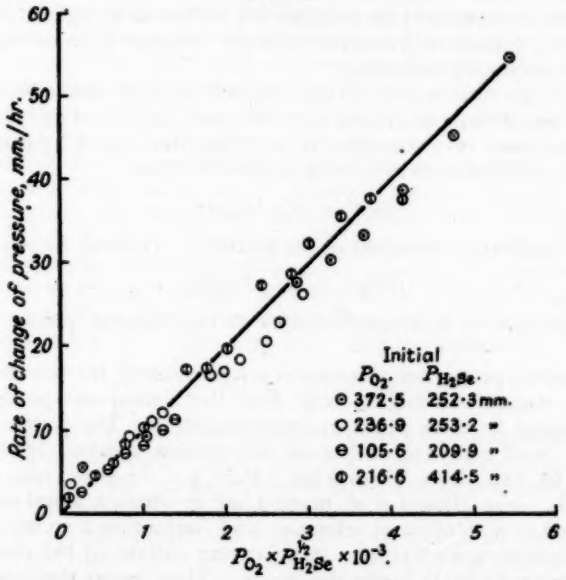
kinetic investigation reported in Part I. The results obtained were not, however, completely satisfactory, for the curves, though linear over the first parts of the experiments, showed an increase of gradient towards the ends. Also, though it is not rendered markedly apparent by this method of plotting, it was observed that the rates showed considerable periodic variation in time.

It was found that much more consistent readings could be made if the experiments were carried out under intermittent illumination, the reaction vessel being illuminated and darkened for alternate periods of one hour. The resulting pressure variations could not easily be examined by plotting the relevant quantity from the integrated rate equation against time. The average rates of change of pressure over the periods of illumination were, therefore, plotted against the products of the mean pressures of oxygen and the square roots of the mean pressures of hydrogen

selenide obtaining over those periods, in a manner similar to that used in the analysis of the measurements made in the isolation experiments. The results of four typical experiments plotted in this way are shown in Fig. 3. The slope of this curve is readily seen to be equal to $\frac{3}{2}k$ and, as its numerical value is $1{\cdot}0 \times 10^3$, the average value of k for the four runs is $6{\cdot}7 \times 10^{-3}$ mm.$^{-\frac{1}{2}}$ hr.$^{-1}$.

The agreement between the various values of k, including those reported in Part I, seems highly satisfactory, particularly as many different selenium films were used over the course of the work. In general, any particular film was used only for three runs, except in the early part of the investigation where sufficient experiments were made, using the same film, to establish that the catalytic activity of the film remained sensibly constant after a minimum thickness had been reached.

FIG. 3.



It might also be pointed out that the increase in the value of k, found in experiments performed under continuous illumination, was not due to a permanent increase in catalytic activity of the selenium film, since values of k for the initial stages of consecutive experiments with the same film were approximately equal. It seemed to arise from some effect which was cumulative in continuous light but decayed in the dark, as is shown by the more uniform behaviour of the system in intermittent light. The behaviour of the system in darkness provides further evidence on this point. In all cases slow reaction occurred in the dark. No correlation between the rate of this dark reaction and corresponding rates under illumination could be established; the relation appeared to depend more on the previous history of the system than on the concentrations of the reactants. However, if this dark rate was measured over a series of short intervals of time subsequent to the shutting off of light from the reaction vessel, it was found to decay rapidly, falling in the course of thirty minutes to about one-third of its initial value and then becoming constant. Such behaviour could be explained by an accumulation of some intermediate product, *e.g.*, selenium dioxide or hydrogen perselenide (cf. Neilsen *et al.*, *J. Amer. Chem. Soc.*, **1939**, **61**, 440), which undergoes further reaction. This however seems unlikely, as no pressure changes were observed when oxygen or hydrogen selenide alone was exposed to light, in the presence of selenium and water, for long periods.

It was shown in Part I that the rate of oxidation depended little upon the wave-length of incident light over the range examined, and because of the experimental conditions it followed that the reaction rate could only vary as some small fractional power of the light intensity. This conclusion was confirmed by further experiments. In these, the reaction vessel was illuminated with filtered light (5790, 5777 A.), relative intensities being measured with a selenium photocell of reasonably linear response in this spectral region. A comparison of the relative rates and relative light intensities is made in Table II.

TABLE II.

Mean P_{O_2}, mm.	Mean P_{H_2Se}, mm.	Rel. light intensity.	dP/dt, mm./hr.
218·6	255·4	100	27·2
215·7	249·7	28	21·4
213·1	244·6	100	26·0
208·4	235·1	44	19·6
205·9	230·2	100	24·0
203·6	225·5	10	16·9
201·4	221·1	100	20·4

Discussion.

It was suggested in Part I that the primary act in this reaction is the absorption of light by selenium and that subsequent stages involve hydroselenide ions or hydrogen ions or both. These entities cannot be concerned in the primary act as there is no light absorption in the visible region by oxygen-free solutions of hydrogen selenide, whereas light of wave-length as long as 5790 A. is effective in promoting oxidation.

The appearance of the square root of the pressure of hydrogen selenide as a term in the kinetic equation may be adduced as evidence for the participation of the products of electrolytic dissociation in the reaction. For example, if the concentration of hydroselenide ions is rate controlling and the hydride behaves as a weak electrolyte, then

$$[HSe^-] = (K_1 . [H_2Se])^{\frac{1}{2}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where K_1 is the first dissociation constant of the hydride. This can be rewritten as

$$[HSe^-] = (K_1 k P_{H_2Se})^{\frac{1}{2}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where P_{H_2Se} is the pressure of hydrogen selenide in the gaseous phase and k is a partition coefficient.

When the photoelectric properties of selenium are considered, the possibility arises that some process analogous to electrolysis might occur with the consequent production of uncharged radicals and that it might be these which undergo oxidation. The system would then act as a photo-galvanic cell. Such cells are not novel (cf. Sabine, *Nature*, 1878, **17**, 512; Minchin, *Proc. Roy. Soc.*, 1895, **58**, 142; Ries, "Das Selen," 1918, J. C. Hubers; von Hippel *et al.*, *J. appl. Physics*, 1946, **17**, 215). von Hippel *et al.* made a cell in which a metal electrode, coated with selenium was immersed in a solution of selenious acid containing a second electrode of a noble metal or a second selenium-coated plate. A polarising voltage of the order of two volts was used, the auxiliary electrode being made the anode. They found that the current generated in such cells was proportional to the intensity of incident light when sufficient polarising voltage was applied, but, when this voltage was decreased, the linearity failed at low intensities, whilst at greater intensities the current became practically constant and independent of light intensity. The electrode processes suggested in this work are :

Cathode (illuminated)	$H_2SeO_3 + 4e^- + 4H^+ = Se + 3H_2O$
Anode (Se)	$Se + 3H_2O = H_2SeO_3 + 4e^- + 4H^+$

It is also pointed out that if other electrolytes were used, *e.g.*, hydrochloric acid, the selenium on the illuminated electrode was stripped off on continued use.

The preliminary working hypothesis that the oxidation under investigation proceeds *via* an electrolytic process, though fitting our observations in a general way, requires elaboration to explain fully the kinetics of the reaction.

A mechanism which seems to account for the observed characteristics is now proposed.

Let it be assumed that the electrons within a crystal of selenium possess a limited power of circulation within the crystal lattice, but that the average density of electrons surrounding the nuclei in the bulk of the lattice must remain fixed. This implies that, owing to dissymmetry at the surface of the crystal, a potential barrier will exist there, preventing the flow of electrons to or from the crystal. This is consistent with the observations of Brown (*Phil. Mag.*, 1914, [vi], **28**, 496) who showed that, when a crystal of selenium was illuminated at certain points, the conductance of the whole crystal was increased, and with the fact that photoelectrons are not emitted from selenium at wave-lengths greater than 2200 A. (Hughes, *Phil. Trans.*, 1912, **212**, *A*, 205).

Consider, then, a film of selenium immersed in a solution of hydrogen selenide in darkness. Let one face of the film be illuminated. Absorption of radiation will decrease the electron

affinity of the surface layer of selenium, and the relative changes of electron affinity with respect to the two ionic species in solution will result in an increased field of force between the hydrogen ions and the face and a decreased field of force between the negative hydroselenide ions and the face. Hydrogen ions will thus become preferentially adsorbed. This circumstance would facilitate the transfer of electrons across the potential barrier and it might be expected that some adsorbed hydrogen ions would be discharged. However, there is no evidence for the production of hydrogen in any of these experiments. In most cases oxidation was carried to completion, and the pressure decrements were found to fit the stoicheiometric requirements of simple oxidation.

An explanation of this can be given as follows. Imagine a hydrogen ion adsorbed at the light face. Owing to the modification by illumination of the potential barrier at this surface an electron is capable of leaving the selenium lattice and discharging this ion, the positive charge produced on the selenium atom adjacent to this former ion being neutralised by a general electron drift towards the light face. What is virtually a hydroselenide radical is formed and this remains incorporated in the lattice structure. Such a system is unstable and a further transfer of an electron to the hydroselenide radical occurs. The increase in volume of the radical on the acquisition of negative charge renders its position in the lattice geometrically untenable and it is expelled as a hydroselenide ion. This does not, however, leave the surface but remains adsorbed there, thus binding one of the two excess positive charges now present on the selenium lattice and forming part of an electrical double layer. The local excess of positive charge on the lattice due to this double layer causes a migration of the second positive charge to regions of lower potential energy—a process reminiscent of the drift of positive " holes " to the dark side of a selenium crystal, so frequently postulated in the discussion of barrier-layer cells.

These ideas may be further expanded. The system consisting of illuminated selenium in contact with an aqueous solution of hydrogen selenide may be considered as a reversible electrode at which an equilibrium, $Se + H^+ + 2e^- \rightleftharpoons HSe^-$, can be established, thus giving rise to a potential

$$E = E_0 + (RT/2F) \ln [H^+]/[HSe^-] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

where $[H^+]$ and $HSe^-]$ are the respective concentrations of hydrogen ions and hydroselenide ions in the solution. E_0 will depend, in some way, on the state of illumination of the system and, as this was kept constant in all the kinetic experiments, E_0 will be constant; also $[H^+] = [HSe^-]$, and therefore E will be constant.

In the establishment of this equilibrium, hydrogen ions will be discharged and hydroselenide ions generated; there will thus be an excess of hydroselenide ions over the demands of electroneutrality, and there will be a migration of positive charge to the dark face, the number of positive charges migrating being equal to the number of hydroselenide ions produced. Hydroselenide ions will therefore become adsorbed at the dark face, forming a double layer at this site. The total number of ions so adsorbed can be calculated as follows.

Let the double layer at the light face possess a fixed electrical capacity C. This assumption is justifiable, since this capacity will be proportional to some function of the light intensity and to the projected area of the illuminated surface, normal to the light beam, both of which were kept constant. The quantity of positive charge produced at this face in the attainment of its equilibrium potential will then be equal to $2E'C$, where E' is the potential across the double layer, which is fixed by the equilibrium potential of the surface. Of this charge, a quantity $E'C$ will migrate to the dark side, and, to a first approximation, $E'C/q$ hydroselenide ions will become adsorbed there, q being the charge on one hydroselenide ion. It should be noted that the number of ions thus adsorbed depends on the conditions at the light face and is in no way a function of the area of the dark face.

Now the ions adsorbed at the dark surface will be in equilibrium with those in the bulk of the solution which possess energy of thermal motion; therefore the distribution of ions between the two phases can be described by the equation

$$n = \text{const.} [c_{sol} \cdot \exp(x/RT)] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

where n = number of HSe^- ions in the adsorbed layer, c_{sol} = concentration of HSe^- ions in solution, x = the energy of binding of one g.-ion of HSe^- ions in the double layer, and R and T have their usual significance.

The binding force, P, between charges in the double layer will be defined by $P = q^2/r^2D$, where q = ionic charge of HSe^-, r = distance of separation of charges in the double layer, and D = a quantity of the nature of dielectric constant.

Thus it may be assumed, as an approximation, that P is constant; it follows that x is constant, and from equation (4) we can write

$$\ln n = \ln c_{sol} + \text{constant}$$

or

$$n = c_{sol} \cdot \text{constant}$$

Consider now the behaviour of such a system towards oxygen. The free hydroselenide ions in solution will not undergo oxidation as no electron acceptor is available, but, if the energy of the electrons produced by oxidation is sufficient to enable them to cross the energy hump on the dark side, oxidation will proceed at this site. Comparison of the free energy change involved in the reaction

$$2HSe^- + \tfrac{1}{2}O_2 = H_2O + 2Se + 2e^-$$

with that of the discharge of hydroselenide ions, indicates that such a potential barrier might act as a discriminating filter between the electrons produced by these two reactions.

It will be seen that the adsorption equilibrium, previously discussed, will remain sensibly unaffected by the reaction proceeding at the dark face. The oxidation does in effect give rise to an electric current flowing between the light and dark faces of the selenium, the circuit outside the selenium layer being completed by the solution. If there is no accumulation of charge at any point in this circuit, which is unlikely if transport effects are ignored, then the existing electrical tensions should remain unchanged and adsorption defects arising from the oxidation should become repaired by the forced diffusion of ions.

This may be restated in a different way. The removal of hydroselenide ions from the dark face by oxidation is equivalent to the removal of positive charge from the selenium layer as a whole, and the potential of the light face will therefore fall. To restore the equilibrium potential defined by equation (3), hydrogen ions will be adsorbed and discharged at this face, as already described, with a consequent reinstatement of the electrical and adsorption conditions previous to the oxidation. This process will be a continuous one, and as oxidation proceeds selenium will actually be dissolved from the light face. For every selenium atom so removed, two selenium atoms will be deposited at the dark side. This gives an explanation of the observations regarding the " dissolution " and " reprecipitation " of selenium noted in Part I. It is understandable that the red modification, which is the least stable, should be first to suffer attack. The stripping of selenium from the cathodes of von Hippel's cells might also be recalled and it can be added that the selenium deposit produced over the course of several experiments always showed considerable etching in the illuminated area.

If this is an adequate description of the mechanism of the oxidation, and if the simplifying assumptions are made that the reaction is of the first order with respect to oxygen and that the system is in continuous equilibrium, then the rate of oxidation can be defined by the expression

$$\text{rate} = k \cdot [HSe^-] \cdot P_{O_2}$$

which is in agreement with experiment.

BIRKBECK COLLEGE, E.C.4.

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389. *A Contribution to the Chemistry, including the Stereochemistry, of the θι-Halogenohydroxystearic Acids.*

By George King.

Improvements have been effected in the preparation and characterisation of the θι-chloro-, -bromo-, and -iodo-hydroxystearic acids. The identity of the halogenohydroxystearic acids prepared from elaidic acid by the addition of the appropriate hypohalogenous acid with those obtained from the epoxide by the addition of the corresponding hydrogen halide has been established. Significant amounts of oily by-products, consisting largely of *ester-acids*, with some dihalides, result by the former method, especially when oleic acid is the starting material.

The conversion of the halogenohydroxystearic acids into the corresponding oxides proceeds smoothly at room temperature in the presence of dilute alkali; however, some dihydroxystearic acid also results when concentrated alkali at 100° is used. Ketonic acids, presumably a mixture of θ- and ι-ketostearic acid, are formed in part by the action of mercuric oxide on the *iodohydroxystearic acids* in moist ether. The dichlorides of oleic and elaidic acids are much more stable towards alkali.

The stereochemical changes involved in the mutual transformations of the two (±)-θι-dihydroxystearic acids are discussed, and the author's original scheme of configurations is modified.

In a previous communication (*J.*, 1942, 387) the mutual transformations of the (±)-θι-dihydroxystearic acids, m. p.s 132° and 95°, by way of the chlorohydroxy- and epoxy-stearic acids, were described, and the dihydroxystearic acid, m. p. 141°, occurring in castor oil was shown to be an optically active component of the acid, m. p. 132°. Configurational formulæ were provisionally assigned to these acids, reasons being adduced for the assumption that an inversion of configuration occurs on hydrolysis of the epoxy- to the dihydroxy-stearic acids. The literature abounds in similar instances of inversions accompanying the opening of the 1 : 2-oxide ring, typical of which are the hydrolyses of epoxy*cyclo*hexane (Brunel, *Bull. Soc., chim.*, 1903, **29**, 884; Derx, *Rec. Trav. chim.*, 1922, **41**, 318), crotonic acid oxide (Braun, *J. Amer. Chem. Soc.*, 1930, **52**, 3179), the anhydro-sugars (Peat, *Ann. Reports*, 1939, **36**, 262), and epoxy-steroids (Shoppee, *Ann. Reports*, 1946, **43**, 212).

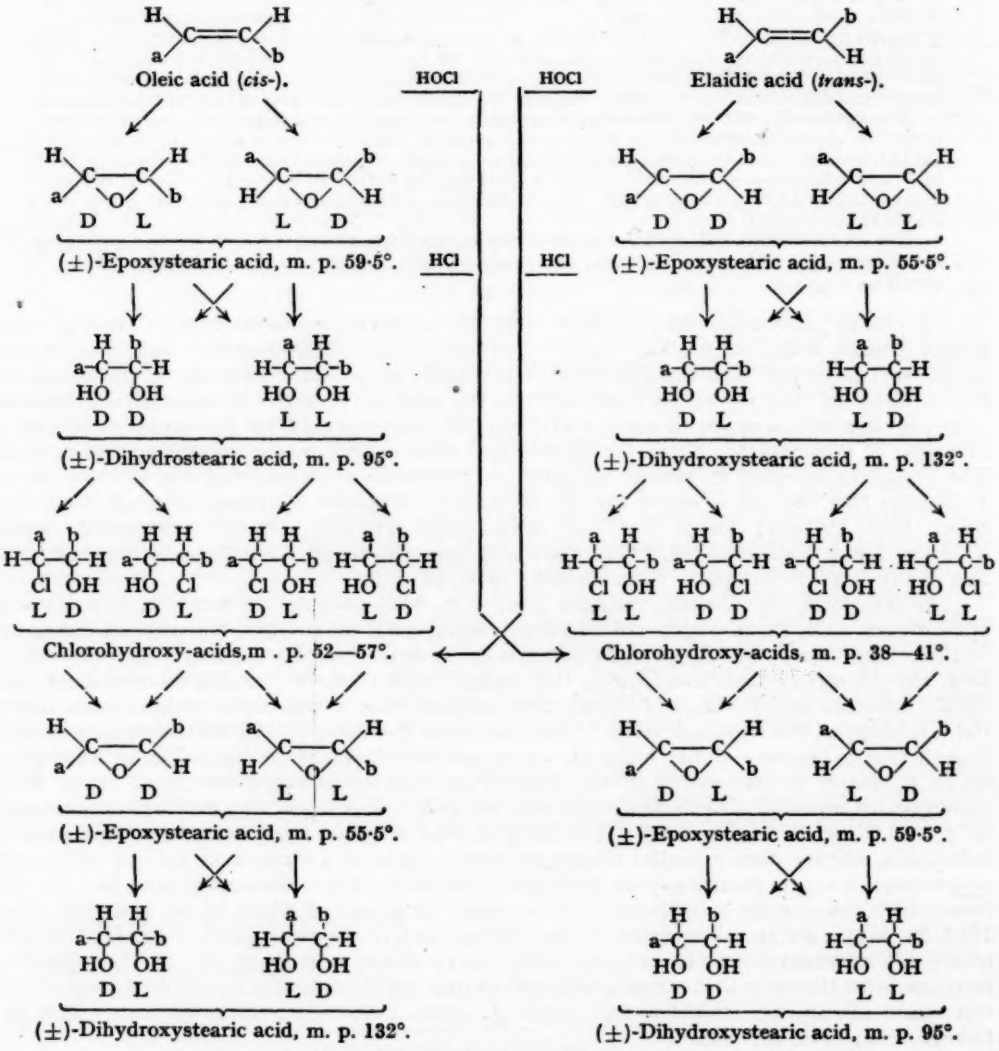
The transformation, dihydroxystearic acid, m. p. 95° ⟶ chlorohydroxystearic acids ⟶ epoxystearic acid, m. p. 55·5° ⟶ dihydroxystearic acid, m. p. 132°, necessitates either one or three inversions. On the grounds that the epoxy-acids combine with hydrogen chloride to form chlorohydroxy-acids from which the original oxides are recoverable on treatment with alkali, Atherton and Hilditch (*J.*, 1943, 204) deduced that a Walden inversion occurs during the first stage of the transformation. They favoured the view, though without cogent reason, that there is no inversion during either the opening or the closure of the oxide ring, an assumption which is clearly at variance with the observation that (+)-epoxystearic acid, m. p. 59·5°, undergoes an inversion of configuration on alkaline hydrolysis to form (±)-dihydroxystearic acid, m. p. 95° (King, *loc. cit.*, p. 389). A striking parallel is afforded by the *cis*-compound maleic acid oxide, which suffers a similar change of configuration on hydrolysis to furnish exclusively (±)-tartaric acid, yet combines with hydrogen chloride to form *r*-chloromalic acid, m. p. 153·5°, from which the original epoxide may be recovered by means of alkali (Kuhn and Ebel, *Ber.*, 1925, **58**, 919). Further, conversion of the optically active dihydroxy-acid, m. p. 141°, by way of the chlorohydroxy- into an *optically active* epoxy-stearic acid (King, *loc. cit.*) is difficult to reconcile with the view that a configurational change occurs only during the first stage of this conversion (cf. Lucas, Schlatter, and Jones, *J. Amer. Chem. Soc.*, 1941, **63**, 22; Lucas and Garner, *ibid.*, 1948, **70**, 990).

It appears highly probable, therefore, that an inversion accompanies *each* of the three stages involved in the mutual transformation of the (±)-dihydroxystearic acids, as suggested by Swern (*ibid.*, 1948, **70**, 1235) from purely general considerations. The annexed scheme, in which the symbols D and L have configurational significance only, indicates clearly the stereochemical changes occurring during these transformations and replaces that originally proposed by the author. It accords with the *trans*-addition of hypochlorous acid to the ethylenic acids and preserves the *erythro*-structure for the dihydroxy-acid, m. p. 132°.

In this connexion, considerable importance attaches to the identity of the chlorohydroxystearic acids resulting from the action of hydrogen chloride on the epoxy-acids with those obtained from the corresponding unsaturated acids by the addition of hypochlorous acid. According to Nicolet and Poulter (*ibid.*, 1930, **52**, 1186) these products differ, the former consisting, in their view, of θ-hydroxy-ι-chloro- and the latter of θ-chloro-ι-hydroxy-stearic acids. Moreover, the union of the oxides with hydrogen chloride in dry ether takes place under

conditions which may well favour the formation of oxonium salts of the type .

In view of the fact that pure chlorohydroxystearic acids have not hitherto been isolated by the hypochlorous acid method, except in very small yield, it was felt desirable to make a further study of these products and of the bromo- and iodo-hydroxystearic acids obtained analogously.



(a = $CH_3 \cdot [CH_2]_7$; b = $[CH_2]_7 \cdot CO_2H$.)

As a result, it has now been found possible to obtain a 50—60% yield of a mixture, melting at 52—57°, of pure θ-chlorohydroxystearic acids by the direct union of elaidic acid with hypochlorous acid in aqueous solution and to establish its identity with the product resulting in nearly theoretical yield from the action of hydrogen chloride on elaidic acid oxide, m. p. 55·5°, in ethereal solution. The former method, however, also furnishes appreciable amounts of oily by-products, consisting apparently of mixtures of *ester-acids*, such as

$$CH_3 \cdot [CH_2]_7 \cdot CHCl \cdot CH(OH) \cdot [CH_2]_7 \cdot CO_2 \cdot CH \begin{cases} [CH_2]_7 \cdot CO_2H \\ CHCl \cdot [CH_2]_7 \cdot CH_3 \end{cases}$$

together with variable proportions of elaidic acid dichloride and other chlorinated products. The evidence for such esters consists largely of analytical values and of the fact that significant

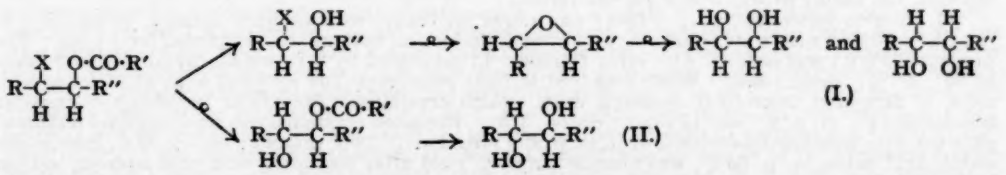
yields of epoxystearic acid can be obtained within a few hours by hot, but not by cold, saponification. If chlorine water is used as a source of hypochlorous acid (cf. Read and Andrews, *J.*, 1921, 1774; Read and Reid, *J.*, 1928, 745, 1487), the dichloride is the principal product, but appreciable amounts of chlorohydroxystearic acids are also formed. Repeated crystallisation of the mixed chlorohydroxy-acids from methanol affords a *product*, melting sharply at 73°, which is probably pure θ-chloro-ι-hydroxy- or ι-chloro-θ-hydroxy-stearic acid. These chlorohydroxystearic acids are quantitatively converted into the oxide, m. p. 55·5°, within two hours by cold aqueous sodium hydroxide.

Similarly, oleic acid oxide, m. p. 59·5°, and ethereal hydrogen chloride furnish a mixture of chlorohydroxy-acids, m. p. 38—41°, stereoisomeric with those prepared from elaidic acid or its oxide, from which the original oxide can readily be recovered by the action of cold alkali. On the other hand, oleic acid and aqueous hypochlorous acid react to give oily products containing less than 40% of free chlorohydroxystearic acid, the remainder consisting of ester-acids of the type already mentioned, oleic acid dichloride, and possibly other chlorinated products. No solid constituent could be isolated from this mixture (cf. Atherton and Hilditch, *loc. cit.*, p. 207), and only small amounts of the oxide are isolable after treatment with alkali, even at 100°.

The chlorohydroxystearic acids crystallise in needles and are very sparingly soluble in hexane or light petroleum at 0°, but those from oleic acid oxide are moderately soluble at room temperature. In contrast, oleic acid dichloride is a viscous oil, m. p. 12—15°, soluble in light petroleum at 0°, whereas elaidic acid dichloride crystallises in well-defined rhombic or six-sided plates, m. p. 47·5° (Piotrowski, *Ber.*, 1890, **23**, 2531, gave m. p. 32°), sparingly soluble in light petroleum at 0°. Further, elaidic acid dichloride is virtually unaffected by prolonged treatment with aqueous alkali at 100° and even oleic acid dichloride is only slowly attacked, forming dihydroxystearic acid, m. p. 95°.

The strictly anhydrous conditions used by Nicolet and Poulter in the preparation of the chlorohydrins from oleic and elaidic acid oxides have been adapted by Swern *et al.* (*Analyt. Chem.*, 1947, **19**, 414) for the quantitative determination of oxirane oxygen $\left(\begin{smallmatrix}C\\C\end{smallmatrix}\!>\!O\right)$, but are unnecessary for preparative purposes. More conveniently, an ethereal solution of the oxide may be shaken with a moderate excess of concentrated aqueous halogen acid for 15—60 minutes. This method has been successfully applied also to the preparation of the bromohydroxystearic acids (m. p. 15—18·5°, from oleic acid oxide; m. p. 56—63°, from elaidic acid oxide) and the *iodohydroxystearic acids* (an oil from oleic acid oxide; needles, m. p. 54—60°, from elaidic acid oxide), thus avoiding the possible reduction of the oxides to unsaturated acids by the prolonged action of anhydrous hydrogen iodide (Morrell and Phillips, *J. Soc. Chem. Ind.*, 1939, **58**, 160τ). The iodo-compounds, especially those derived from oleic acid oxide, are rather unstable and slowly lose iodine. When shaken in moist ether with freshly precipitated mercuric oxide, they are partly converted into a mixture, m. p. 73—74·5°, of ketonic (probably θ- and ι-ketostearic) acids.

The preparation of the bromo- and iodo-hydroxystearic acids from the ethylenic acids by the action of hypobromous and hypoiodous acid, respectively, is less satisfactory, and the subsequent isolation and purification of the oleic acid derivatives appear impracticable (the elaidic acid derivatives are more tractable). The yields of free halogenohydroxy-acids are relatively small, the principal products being oily ester-acids, with variable amounts of dihalide. As might be expected, the hydrolysis of these esters leads to different products according to the firmness with which the halogen is held:



Thus, whilst the more firmly held chlorine yields exclusively the oxide and its hydrolysis product (I), the less stable bromo- and iodo-compounds give rise in addition to significant amounts of the stereoisomeric dihydroxy-acid (II), the oxide normally predominating. Accordingly, the products of the action of hypochlorous acid on oleic acid afford on hydrolysis the oxide, m. p. 59·5°, with a small amount of the corresponding dihydroxystearic acid, m. p. 95°; those from elaidic acid afford the oxide, m. p. 55·5°, and the dihydroxy-acid, m. p. 132°. On

the other hand, the crude products of the action of hypobromous and hypoiodous acids on oleic acid yield the oxide, m. p. 59·5°, and a *mixture* of the two dihydroxy-acids, whilst those from elaidic acid give the oxide, m. p. 55·5°, and the two dihydroxy-acids.

In the light of these results, it seems highly probable that the rise in the proportion of the lower-melting dihydroxy-acid, reported by Esafov (*J. Gen. Chem., Russia*, 1937, **7**, 1403) to occur when the concentration of alkali used to hydrolyse the iodohydrin of oleic acid is increased, may be ascribed to the progressive hydrolysis of the epoxide, m. p. 59·5°, and that the presence of the higher-melting dihydroxy-acid among the products arises from saponification of esters in his "iodohydrin" preparation. There is no evidence that mixtures of the two oxides or of the dihydroxystearic acids result from the hydrolysis, however effected, of the pure halogenohydroxystearic acids obtained by the action of the halogen acid on an epoxystearic acid, and the latter reaction may be regarded as substantially homogeneous in the stereochemical sense.

Careful re-examination of the oxides of oleic and elaidic acids has confirmed the accuracy of the m. p.s and crystalline appearances recorded by Ellis (*Biochem. J.*, 1936, **30**, 756). Ethyl oleate oxide, prepared from ethyl oleate and peracetic acid, was found to melt at 21°, in agreement with the value found by Pigulevski and Rubaschko (*J. Gen. Chem. Russia*, 1939, **9**, 830).

Experimental.

Chlorohydroxystearic Acids from Elaidic Acid.—(*a*) 0·3M-Sodium hypochlorite solution (150 ml.; prepared by passing chlorine into saturated aqueous sodium hydrogen carbonate) was added to a solution of elaidic acid (10 g.) in 0·04N-potassium hydroxide (1 l.). The solution was saturated with carbon dioxide, set aside overnight, and then slowly acidified with dilute sulphuric acid, excess of hypochlorous acid being destroyed by sodium sulphite. Crystallisation of the semi-solid product from *n*-hexane gave a mixture of nearly pure chlorohydroxystearic acids (6·8 g.) as needles, m. p. and mixed m. p. with the similar product prepared from elaidic acid oxide 52—57° (Found: C, 64·1; H, 10·5; Cl, 11·1; equiv., 335. Calc. for $C_{18}H_{35}O_3Cl$: C, 64·5; H, 10·5; Cl, 10·6%; equiv., 335). Recrystallisation from light petroleum–benzene and repeated crystallisation from methanol gave a *product*, melting sharply at 73·5°, which was probably pure θ-chloro-ι-hydroxy- or ι-chloro-θ-hydroxystearic acid (Found: C, 64·5; H, 10·3; Cl, 10·8%).

The mixed chlorohydroxystearic acids (2 g.) were dissolved in an excess of cold 0·1N-sodium hydroxide; after 2 hours acidification afforded a nearly theoretical yield (1·78 g.) of elaidic acid oxide, which separated from ethanol in small rhombic plates, m. p. and mixed m. p. 55·5° (Found: C, 72·2; H, 11·4; equiv., 299. Calc. for $C_{18}H_{34}O_3$: C, 72·4; H, 11·5%; equiv., 298).

On evaporation, the hexane mother-liquor left a viscous oil (4 g.), which was completely soluble in cold, very dilute alkali, *ca.* 60% apparently consisting of a mixture of *ester-acids* of the types

$$OH\cdot CHR\cdot CHCl\cdot[CH_2]_7\cdot CO_2\cdot CHR\cdot CHCl\cdot[CH_2]_7\cdot CO_2H \text{ and}$$
$$CHRCl\cdot CHCl\cdot[CH_2]_7\cdot CO_2\cdot CHR\cdot CHCl\cdot[CH_2]_7\cdot CO_2H$$

(R = $CH_3\cdot[CH_2]_7$·), 35% of elaidic acid dichloride, and 1·3% of elaidic acid (Found: C, 65·8; H, 10·3; Cl, 11·0; equiv., 500; I.V., 1·2. $C_{36}H_{68}O_5Cl_2$ requires C, 66·3; H, 10·5; Cl, 10·9; equiv., 652. $C_{36}H_{67}O_4Cl_3$ requires C, 64·5; H, 10·1; Cl, 15·9; equiv., 670. Calc. for $C_{18}H_{34}O_2Cl_2$: C, 61·2; H, 9·7; Cl, 20·1%; equiv., 353). The following data were also used in computing the probable composition of the oil, since α-chlorohydrin groups are quantitatively converted into epoxy-groups by cold alkali, and hot saponification of the esters leads to the transitory generation of α-chlorohydrins without measurably affecting the dichloride: (i) sodium hydroxide required for immediate neutralisation, 1·998; (ii) total alkali neutralised in 2 hours at 20°, 2·900; (iii) total alkali neutralised in 2 hours at 100°, 4·802; (iv) chlorine saponified in 2 hours at 20°, 0·930; (v) chlorine saponified in 2 hours at 100°, 1·947 milli-equivs./g. No significant amount of epoxystearic acid was isolated after saponifying the oil in the cold for 2 hours, but hot saponification furnished a fatty solid, which was resolved by light petroleum (b. p. 40—60°) into (i) very sparingly soluble dihydroxystearic acid (3%), crystallising from methanol in rhombic and hexgonal plates, m. p. 125—127·5°, (ii) nearly pure elaidic acid oxide (50%), m. p. and mixed m. p. 54—55°, which separated from the solvent at 0°, and (iii) a soluble, semi-crystalline fraction, the nature of which was not determined.

(*b*) Chlorine water (900 ml.; 0·184N) was added gradually, with vigorous shaking, to elaidic acid (20 g.) emulsified with water (200 ml.) at 50°, and mechanical shaking was continued for 1 hour. The product (23·9 g.) was isolated with ether (Found: Cl saponified by 0·1N-sodium hydroxide in 2 hours at 20°, 2·7%; equiv., 434). When dissolved in light petroleum (200 ml.) and kept at 0° for several days, it deposited chlorohydroxystearic acids, which crystallised from light petroleum–benzene in needles (3·5 g.), m. p. 52—60° (Found: equiv., 333). Repeated crystallisation from aqueous methanol gave the pure chlorohydroxystearic acid, m. p. and mixed m. p. 73·5° (Found: equiv., 334), from which elaidic acid oxide, m. p. 55·5°, was obtained in 96% yield after treatment with cold aqueous sodium hydroxide.

Removal of solvent from the light petroleum mother-liquor left an oil (18·8 g.), which became semi-crystalline within several weeks and appeared to contain about 60% of ester-acids (Found: Cl saponified by N-sodium hydroxide in 2 hours at 20°, 1·2, and in 2 hours at 100°, 5·1%; equiv., 456; I.V., 1·3). It afforded a 12% yield of elaidic acid oxide, m. p. 54°, on hot saponification. The semi-crystalline product (5 g.) was drained on a porous plate, and the solid (1·45 g.) was crystallised successively from acetic acid and acetone, giving elaidic acid dichloride (0·65 g.) in elongated hexagonal or nearly rectangular plates, m. p. and mixed m. p. 47° (Found: equiv., 357).

Chlorohydroxystearic Acids from Elaidic Acid Oxide.—Elaidic acid oxide (3 g., m. p. 55·5°) in ether (30 ml.) was shaken vigorously from time to time during 1 hour with 10N-hydrochloric acid (2 ml.). Evaporation of the washed and dried ethereal solution left a residue of chlorohydroxystearic acids, which crystallised from light petroleum–benzene in needles (2·85 g.), m. p. and mixed m. p. with the similar product prepared from elaidic acid 52—57° (Found: C, 64·5; H, 10·3; Cl, 10·6%; equiv., 334). The product gave no precipitate when boiled for a short time with alcoholic silver nitrate, which indicates the absence of an oxonium chloride. It afforded a nearly theoretical yield of the original oxide on treatment with 0·1N-sodium hydroxide for 2 hours at room temperature.

Chlorohydroxystearic Acids from Oleic Acid Oxide.—An ethereal solution of oleic acid oxide (3 g.; m. p. 59·5°), shaken with concentrated hydrochloric acid as above, gave a mixture of chlorohydroxystearic acids (3·3 g.), which crystallised (from light petroleum containing 5% of ether) in minute rectangular plates or tablets, m. p. 38—41° (Found: C, 64·3; H, 10·4; Cl, 10·9%; equiv., 333). With cold alkali the product afforded a 95% yield of the original oxide, separating from acetone in characteristic long, thin laminæ, m. p. 59·5°.

Action of Hypochlorous Acid on Oleic Acid.—(*a*) A solution of oleic acid (5 g.; I.V., 90·5; equiv., 283) in the theoretical amount of aqueous sodium hydroxide was treated with sodium hypochlorite and carbon dioxide according to Atherton and Hilditch's method (*J.*, 1943, 207). The oily product (5·83 g.) became very viscous at 0°, but did not crystallise. It was resolved by light petroleum at 0° into (i) a sparingly soluble fraction (2·73 g.) (Found: C, 61·5; H, 9·6; Cl, 13·6%; equiv., 425; I.V., 1·9) and (ii) a soluble fraction (3·1 g.) (Found: C, 66·0; H, 10·8; Cl, 11·5%; equiv., 398; I.V., 1·5), neither of which furnished any crystalline matter. After saponification with N-sodium hydroxide for 2 hours at 100°, both fractions gave semi-solid products, which were separated by light petroleum into (i) a trace of sparingly soluble dihydroxystearic acid, which crystallised from methanol in nearly rectangular plates, m. p. and mixed m. p. 93—94°, (ii) crude oleic acid oxide (9—12%), m. p. 54—56°, lowered to 48—49° by elaidic acid oxide, raised to 57—58·5° by pure oleic acid oxide, and (iii) a semi-solid fraction, soluble in light petroleum at 0° and containing a little halogen.

(*b*) Oleic acid (5 g.), treated with hypochlorous acid as in the case of elaidic acid [method (*a*)], yielded an oil, of which a fraction (2·24 g.) separated from light petroleum at room temperature (Found: C, 61·5; H, 9·7; Cl, 15·6%; equiv., 427; I.V., 1). Saponification of this fraction at 100° yielded only 4% of oleic acid oxide. Quantitative data obtained by saponification at room temperature and at 100° indicated that the oil consisted mainly of ester-acids, with oleic acid dichloride and possibly other chlorinated products.

Bromohydroxystearic Acids from Elaidic Acid.—(*a*) 0·35M-Sodium hypobromite (100 ml.; prepared from bromine and aqueous sodium carbonate) was added to a solution of elaidic acid (5 g.) in 0·1N-potassium hydroxide (200 ml.), and after 30 minutes the solution was acidified with dilute sulphuric acid, free bromine being destroyed by sodium sulphite. Ether extraction gave an oil, which was dissolved in light petroleum (75 ml.) and cooled at 0° for 2 days. The deposit of bromohydroxystearic acids (1·64 g.) crystallised from *n*-hexane in needles, m. p. and mixed m. p. with the similar product prepared from elaidic acid epoxide 57—61° (Found: Br, 20·9; equiv., 376. Calc. for $C_{18}H_{35}O_3Br$: Br, 21·1%; equiv., 379), and afforded pure elaidic acid oxide, m. p. 55·3°, in 95% yield on treatment with 0·2N-sodium hydroxide for 1 hour at room temperature.

Evaporation of the light petroleum mother-liquor left a semi-crystalline residue (4·3 g.) (Found: Br saponified by N-potassium hydroxide in 2 hours at 100°, 9·8%; equiv., 390; I.V., 38), of which the crystalline component was elaidic acid, m. p. and mixed m. p. 43·5°. The products of saponification of the semi-crystalline residue were resolved by *n*-hexane into (i) about 4% of dihydroxystearic acids, consisting almost entirely of the acid, m. p. 95°, (ii) 14% of elaidic acid oxide, m. p. and mixed m. p. 54—55°, and (iii) a large fraction, soluble in hexane, composed of crude elaidic acid.

(*b*) 1·08M-Hypobromous acid (25 ml.; prepared by adding 10 ml. of bromine to a suspension of 30 g. of freshly precipitated mercuric oxide in 50 ml. of water and filtering) was added gradually, with cooling and shaking, to elaidic acid (5·64 g.) in ether (50 ml.). The ethereal layer was washed, dried, and evaporated, and the residual oil was dissolved in light petroleum (50 ml.) and cooled at 0° for 24 hours. The deposit of bromohydroxystearic acids (1·02 g.) crystallised from light petroleum–benzene in needles, m. p. 66—68°, raised by repeated crystallisation from hexane to 70—71° (Found: equiv., 369; Br, 20·9%).

The light petroleum mother-liquor left an *oil* on evaporation (Found: equiv., 651; Br saponified by 0·1N-sodium hydroxide in 2 hours at 20°, 7·0, and in 4 hours at 100°, 18·5%. $C_{36}H_{68}O_3Br_2$ requires equiv., 741; Br, 21·6. $C_{36}H_{67}O_4Br_3$ requires equiv., 804; Br, 29·8. Calc. for $C_{18}H_{34}O_3Br_2$: equiv., 442; Br, 36·1%). Quantitative data obtained by saponification at room temperature and at 100° indicated that the oil consisted mainly of ester-acids, with a small amount of elaidic acid dibromide. Saponification for 2 hours in the cold gave an insignificant amount of elaidic acid oxide, but after hot saponification the oil (3·6 g.) afforded a solid product, resolved by *n*-hexane into (i) an insoluble fraction (0·77 g.), crystallising from acetic acid and from methanol in rectangular plates (dihydroxystearic acid), m. p. 93°, from whose mother-liquors a few mg. of dihydroxystearic acid, m. p. 127°, were isolated, and (ii) nearly pure elaidic acid oxide (1·23 g.), m. p. 54—55°, depressed to 49—51° by oleic acid oxide. No oleic acid oxide was detected and, when the epoxide was heated with 2½ parts of acetic acid at 100° for 1 hour and the resulting solution was diluted and heated with an excess of 10% aqueous sodium hydroxide for 1 hour, a good yield of nearly pure dihydroxystearic acid, m. p. 130°, was obtained.

Bromohydroxystearic Acids from Elaidic Acid Oxide.—The epoxide (3 g.), m. p. 55·5°, in ether (30 ml.) was shaken frequently during 1 hour with 46—48% hydrobromic acid (3 ml.). The bromohydroxystearic acids (3·79 g.) crystallised from *n*-hexane in needles, m. p. 56—63° (Found: equiv., 376; Br, 21·2%), raised by repeated crystallisation to 70—71° (cf. Morrell and Phillips, *J. Soc. Chem. Ind.*, 1940, **59**, 144T), unchanged on admixture with the similar product from elaidic acid and hypobromous acid. Cold alkali afforded a nearly theoretical yield of the original oxide.

Bromohydroxystearic Acids from Oleic Acid Oxide.—The oxide (3 g.), m. p. 59·5°, gave an oily mixture of bromohydroxystearic acids (3·76 g.), which, when cooled, set to a mass of colourless crystals,

m. p. 15—18·5° (Found: equiv., 379; Br, 21·1%), slightly soluble in light petroleum at 20°. The original oxide was recovered in good yield after treatment with cold aqueous alkali.

Action of Hypobromous Acid on Oleic Acid.—Oleic acid (5·64 g.) in ether (50 ml.) was treated with hypobromous acid as for elaidic acid, method (*b*). Removal of the ether left an oil (7·38 g.) (Found: equiv., 514; I.V., 1·9; Br saponified by 0·1N-sodium hydroxide in 2 hours at 20°, 9·2, and in 4 hours at 100°, 17·8%), which appeared to contain a considerable proportion of ester-acids and could not be purified by fractionation from light petroleum. Oily products were obtained after cold saponification, but hot saponification of the oil (4·05 g.) furnished a solid (3·21 g.), from which were isolated (i) dihydroxystearic acid (0·2 g.), m. p. and mixed m. p. 130—131°, (ii) dihydroxystearic acid (0·1 g.), m. p. and mixed m. p. 93—94°, and (iii) slightly impure oleic acid oxide (0·7 g.), m. p. and mixed m. p. 58—58·5°. No elaidic acid oxide was found.

Iodohydroxystearic Acids from Elaidic Acid.—Iodine (5·08 g.) was added gradually, with shaking, to elaidic acid (5·64 g.) in moist ether (30 ml.), containing freshly precipitated mercuric oxide (2·3 g.) in suspension, and shaking was continued for a further 15 minutes. The ethereal solution was washed successively with aqueous sodium sulphite and water, and then saturated with hydrogen sulphide to remove mercury. The filtered solution was washed with aqueous potassium iodide and with water, dried, and freed from solvent. The residual oil, dissolved in light petroleum (80 ml.) and cooled at 0° for several days, deposited mixed *iodohydroxystearic acids* (2·37 g.), crystallising from *n*-hexane in colourless needles (1·22 g.), m. p. 61—64°, raised by repeated crystallisation from aqueous methanol to 64·5—65·5° (Found: I, 28·2; equiv., 414. $C_{18}H_{35}O_3I$ requires I, 29·8%; equiv., 426). The iodohydroxy-acids were rapidly attacked by an excess of cold 0·1N-sodium hydroxide, making an accurate determination of the equivalent weight difficult, and after 1 hour acidification afforded a nearly theoretical yield of elaidic acid oxide.

Evaporation of the light petroleum mother-liquor left an unstable oil (Found: equiv., *ca.* 438; I saponified by 0·1N-sodium hydroxide in 1½ hours at 20°, 17·5, and by 0·5N-alkali in 2½ hours at 100°, 24·1%). Saponification of the oil (1 g.) at 100° gave a solid product, from which were isolated (i) dihydroxystearic acid (0·09 g.), m. p. 94—95°, with traces only of the higher-melting dihydroxy-acid, (ii) elaidic acid oxide (0·12 g.), m. p. and mixed m. p. 54—55°, and (iii) elaidic acid (0·1 g.), m. p. and mixed m. p. 43—44°. The oil became dark brown and semi-solid in several weeks and was not further examined.

In this method of preparing the iodohydroxystearic acids, prolonged contact with an excess of mercuric oxide was avoided, since this led to the formation of appreciable amounts of ketonic acids (see below).

Iodohydroxystearic Acids from Elaidic Acid Oxide.—66% Hydriodic acid (3 ml.) was added gradually, with cooling and shaking, to the oxide (3 g.), m. p. 55·5°, in ether (30 ml.), and the solution was then shaken occasionally during 1 hour. The recovered iodohydroxystearic acids (4·16 g.) crystallised from *n*-hexane in small needles, m. p. 54—60°, not depressed by the similar product (m. p. 61—64°) prepared from elaidic acid (Found: C, 51·2; H, 8·2; I, 29·8; equiv., 398; I.V., 2. Calc. for $C_{18}H_{35}O_3I$: C, 50·7; H, 8·3; I, 29·8%; equiv., 426). Treatment of the product with cold 0·1N-sodium hydroxide for 30 minutes afforded the original oxide in 95% yield.

Iodohydroxystearic Acids from Oleic Acid Oxide.—When oleic acid oxide (3 g.) in ether was treated with hydriodic acid as above, the product consisted of a viscous oily mixture of *iodohydroxystearic acids* (4·12 g.), which did not solidify at 0° (Found: C, 51·8; H, 8·4; I, 29·4%; equiv., 418; I.V., 3). It became a dark brown semi-solid mass after several weeks, with loss of iodine. Treatment of the oil with cold aqueous alkali for 30 minutes furnished the original oxide in more than 90% yield. Saponification of the oil (1 g.) with 0·5N-potassium hydroxide at 100° for 9 hours led, on acidification, to a solid (0·72 g.), from which dihydroxystearic acid (0·17 g.), m. p. 93—94°, and oleic acid oxide (0·4 g.), m. p. 58—58·5°, were isolated. The same products were obtained when 8N-potassium hydroxide was used for saponification, and no higher-melting dihydroxy-acid was detected (cf. Esavof, *loc. cit.*).

Action of Hypoiodous Acid on Oleic Acid.—Freshly precipitated mercuric oxide (3·25 g.) was added gradually, with cooling and shaking, to a solution of oleic acid (8·46 g.) and iodine (7·62 g.) in moist ether (50 ml.). After further shaking for 30 minutes, the solution was filtered, washed, dried, and evaporated under reduced pressure. The residual oil (11 g.) soon began to decompose and purification was impracticable (Found: equiv., 487; I saponified by 0·1N-sodium hydroxide in 1 hour at 20°, 12·9, and by 0·5N-alkali in 3½ hours at 100°, 20·2%). It probably contained less than 43% of free iodohydroxystearic acids, but an appreciable proportion of ester-acids. Cold saponification gave oily products, but saponification of the oil (5 g.) at 100° furnished a pale yellow, sticky solid (4·15 g.), which was resolved into (i) dihydroxystearic acid (0·2 g.), m. p. 130°, (ii) dihydroxystearic acid (0·15 g.), m. p. 93°, (iii) oleic acid oxide (0·4 g.), m. p. 58°, and (iv) a pale yellow fatty material containing ketonic substances, which gave an oily precipitate with Brady's reagent. No elaidic acid oxide was found.

Elaidic Acid Dichloride.—A 2·1N-solution (34 ml.) of chlorine in dry carbon tetrachloride was added gradually, with cooling, to elaidic acid (9·2 g.) in carbon tetrachloride (30 ml.). After a few minutes, excess of chlorine was destroyed by sodium sulphite. Removal of the solvent left elaidic acid dichloride (11·5 g.), which crystallised from acetic acid and then from acetone, in elongated hexagonal or nearly rectangular plates, m. p. 47·5°, soluble in light petroleum at room temperature, but rather sparingly so at 0° (Found: C, 61·4; H, 9·7; Cl, 19·1; equiv., 354. Calc. for $C_{18}H_{34}O_2Cl_2$: C, 61·2; H, 9·7; Cl, 20·1%; equiv., 353). When the dichloride was boiled with 0·5N-potassium hydroxide for 4 hours, the amount of chlorine saponified was negligible; even after 30 hours' boiling with 2N-alkali, most of the dichloride was recovered unchanged.

Oleic Acid Dichloride.—Oleic acid dichloride, prepared similarly, consisted of a viscous oil, m. p. 12—15°, soluble in light petroleum at 0° (Found: C, 62·7; H, 9·7; Cl, 18·4%; equiv., 402; I.V., 4). Saponification of the dichloride with 2N-potassium hydroxide at 100° for 30 hours afforded a semi-solid product, containing a little dihydroxystearic acid, m. p. 95°, but no significant amount of oxide. The amount of chlorine saponified was 6·2%, or about one-third of the total chlorine.

Action of Mercuric Oxide on the Iodohydroxystearic Acids.—Freshly precipitated mercuric oxide

(2·5 g.) was shaken for 4 hours with a solution of iodohydroxystearic acids (2·5 g.), m. p. 54—60° (prepared from elaidic acid oxide), in moist ether (50 ml.). The filtered solution was washed, dried, and evaporated, leaving a solid (0·5 g.) which crystallised from alcohol in ill-defined plates, m. p. 52—55°, containing elaidic acid oxide and some ketonic material. The insoluble residue of mercury compounds and mercuric oxide was shaken vigorously with ether and dilute sulphuric acid at frequent intervals during several hours. The material (0·87 g.) from the ethereal extract was resolved by *n*-hexane into (i) a few mg. of dihydroxystearic acid, m. p. 130°, (ii) ketonic acids (presumably θ- and ι-ketostearic acids) (0·4 g.), which separated from the solvent at room temperature and crystallised from alcohol in rhombic plates, m. p. 73—74·5° (Found : C, 71·6; H, 10·9; equiv., 296. Calc. for $C_{18}H_{34}O_3$: C, 72·4; H, 11·5%; equiv., 298) (cf. Robinson and Robinson, *J.*, 1926, 2204), and (iii) elaidic acid oxide (0·33 g.), m. p. and mixed m. p. 54—55°, which separated from the cooled solvent.

Repeated crystallisation of the semicarbazones of the ketonic acids from acetone and from alcohol gave hexagonal tablets or short prisms, m. p. 120° (Found : N, 11·4. Calc. for $C_{19}H_{37}O_3N_3$: N, 11·8%). No ketonic acids were obtained when elaidic acid oxide in ether was shaken with mercuric oxide, and there was no evidence of isomerisation of the oxide under these conditions.

The oily iodohydroxystearic acids (2·5 g.), prepared from oleic acid oxide, similarly afforded (i) ketonic acids (0·5 g.), m. p. and mixed m. p. 73° (semicarbazone, m. p. and mixed m. p. 120°), and (ii) somewhat impure oleic acid oxide (0·5 g.), m. p. 55—56°, lowered to 49—50° by admixture with elaidic acid oxide.

Ethyl Oleate Oxide.—Ethyl oleate (30 g.; b. p. 179—182°/3·5 mm.; I.V., 83) was stirred for 2½ hours at 25—30° with 1·3M-peracetic acid (100 ml.) (Findley, Swern, and Scanlan, *J. Amer. Chem. Soc.*, 1945, **67**, 412), and after a further 3½ hours the solution was poured into cold water (1·5 l.). The oil was crystallised twice from ether at −50° and then from light petroleum at the same temperature, giving the pure, crystalline oxide (13 g.), m. p. 21° (Found : C, 73·6; H, 11·6; sap. val., 174. Calc. for $C_{20}H_{38}O_3$: C, 73·6; H, 11·7%; sap. val., 172).

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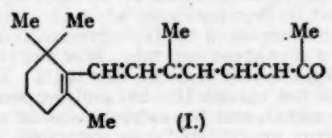
390. *Studies in the Polyene Series. Part XXIX. Ethoxyacetylenic Carbinols and their Conversion into αβ-Unsaturated Aldehydes and Acids.*

By Sir Ian Heilbron, E. R. H. Jones, M. Julia, and B. C. L. Weedon.

Condensation of ethoxyacetylene with acetone, methyl vinyl ketone, and β-ionone gives carbinols which, by semihydrogenation of the triple bond and treatment of the resulting ethoxyvinylcarbinols with dilute mineral acids, are converted into the αβ-unsaturated aldehydes (VII; R = Me), (VII; R = CH_2:CH), and β-ionylideneacetaldehyde (IV), respectively.

A novel synthesis of αβ-unsaturated acids from ketones is described. Hydration of the ethoxyacetylenic carbinols derived from acetone, methyl vinyl ketone, benzylideneacetone, β-ionone, and the C_{15} ketone (X) occurs readily in the presence of dilute mineral acids, giving esters which, on hydrolysis, yield the αβ-unsaturated acids (VIII; R = Me), (VIII; R = CH_2:CH), (IX), β-ionylideneacetic acid (XI), and the C_{17} acid (XII), respectively.

A new method for the preparation of polyene aldehydes was developed by Arens and van Dorp (*Nature*, 1947, **160**, 189) who showed that condensation of ethoxyacetylene with the C_{18} ketone (I) gave the carbinol (II) which, by semihydrogenation of the triple bond and treatment of the ethoxyvinylcarbinol thus formed with dilute hydrochloric acid, was converted into vitamin A aldehyde (III) (retinene$_1$, cf. Morton *et al.*, *Nature*, 1944, **153**, 69, 405). Similarly, β-ionone yielded β-ionylideneacetaldehyde (IV). Since no details of this latter conversion have been published subsequently by Arens and van Dorp, we have repeated this preparation and also applied the method to both acetone and methyl vinyl ketone, each of which reacted readily



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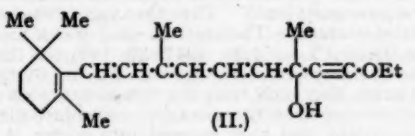

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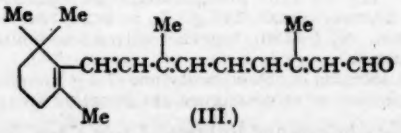

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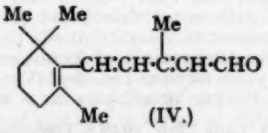
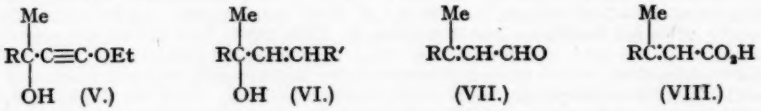


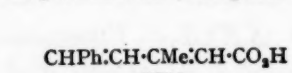
(IV.)

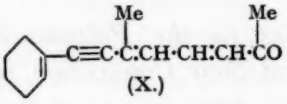
with ethoxyacetylenylmagnesium bromide giving 1-*ethoxy*-3-*methylbut*-1-*yn*-3-*ol* (V; R = Me) and 1-*ethoxy*-3-*methylpent*-4-*en*-1-*yn*-3-*ol* (V; R = CH_2:CH), respectively, in 60 and 30% yield.

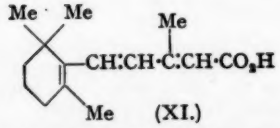
Partial hydrogenation of these carbinols, and treatment of the resulting ethoxyvinylcarbinols (VI; R = Me; R′ = OEt) and (VI; R = CH_2:CH; R′ = OEt) with dilute mineral acids, yielded β-methylcrotonaldehyde (VII; R = Me) and 3-methylpenta-2 : 4-dien-1-al (VII; R = CH_2:CH), respectively. It has previously been reported (Jones and Weedon, *J.*, 1946, 937) that the chlorovinylcarbinol (VI; R = Me, R′ = Cl) also gives β-methylcrotonaldehyde on treatment with dilute sulphuric acid.

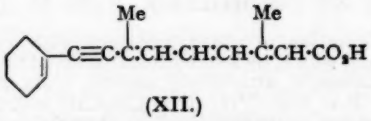


The ease with which alkoxy- and phenoxy-acetylenes are hydrated in the presence of acids (Jacobs *et al.*, *J. Amer. Chem. Soc.*, 1940, **62**, 1849; 1942, **64**, 223; Favorski and Schtschukina, *J. Gen. Chem. Russia*, 1945, **15**, 385) prompted an investigation of the behaviour of ethoxyacetylenic carbinols under similar conditions. It was observed that on shaking an ethoxyacetylenic carbinol, *e.g.*, (V), with 10% sulphuric acid for a few minutes, an ester was formed which, after hydrolysis, yielded an αβ-unsaturated acid, *e.g.*, (VIII). Thus the carbinol (V; R = Me) gave β-methylcrotonic acid (VIII; R = Me) in 55% yield. In order to avoid the losses involved in attempted isolation of the ethoxyacetylenic carbinols, it was advantageous in the majority of cases to convert the crude products obtained by condensation of ketones with ethoxyacetylene directly into the acids. In this manner methyl vinyl ketone, benzylideneacetone, β-ionone, and the C_{15} ketone (X) were converted into *2-methylbuta-1 : 3-diene-1-carboxylic acid* (VIII; R = CH_2:CH) (35%), 4-phenyl-2-methylbuta-1 : 3-diene-1-carboxylic acid (IX) (65%), β-ionylideneacetic acid (XI), and the C_{17} acid (XII) (cf. Heilbron, Jones, and Richardson, *J.*, 1949, 287), respectively.









This new synthesis of αβ-unsaturated acids from ketones thus constitutes an alternative method to the well known Reformatsky reaction with ethyl bromoacetate.*

Condensation of methyl vinyl ketone with zinc and ethyl bromoacetate gave, after dehydration and hydrolysis of the crude hydroxy-ester, the acid (VIII; R = CH_2:CH), identical with that prepared in the manner described above.

Experimental.

Light-absorption measurements were carried out in ethanol except where stated otherwise.

Ethoxyacetylene (cf. Jacobs, Cramer, and Hanson, *J. Amer. Chem. Soc.*, 1942, **64**, 223, 2635).—Bromoethoxyethylene (25 g.), prepared from dibromoacetal by the method of Jacobs *et al.* (*loc. cit.*, p. 223), was placed in a distilling flask (100 c.c.) and the free space in the bulb of the flask almost completely filled with powdered potassium hydroxide. The temperature of the flask and contents was slowly raised to 90—100° whereupon crude ethoxyacetylene (6—8 g.) distilled; b. p. 50°, n_D^{20} 1·395 (Favorski and Shostakovski, *J. Gen. Chem. Russia*, 1943, **13**, 1, give b. p. 48—50°; Jacobs *et al.*, *loc. cit.*, give n_D^{20} 1·3812 for the pure acetylene). The ethoxyacetylene was used without further purification.

Dibromoacetal.—The method used was a modification of that employed by Wizinger and Yousef-el-Attar (*Helv. Chim. Acta*, 1947, **30**, 189) for the preparation of monobromoacetal. Bromine (1060 g.) was added dropwise with vigorous stirring to paraldehyde (225 g.), cooled in an ice–salt bath. The rate of addition was such that the temperature of the mixture did not exceed 10—15° and no permanent colour developed in the mixture. Absolute alcohol (1 l.) was added, and the mixture was set aside at 20° overnight and then poured into water (4 l.). The oil thus precipitated was separated, washed thoroughly with water, dried, and distilled, giving dibromoacetal (350 g.), b. p. 102—104°/15 mm., n_D^{22} 1·4845 (Jacobs *et al.*, *loc. cit.*, give b. p. 94—97°/12 mm., n_D^{25} 1·4790), together with a low-boiling fraction (190 g.) consisting mainly of mono- and di-bromoacetal.

1-Ethoxy-3-methylbut-1-yn-3-ol (V; R = Me).—A solution of ethoxyacetylene (7·4 g.) in ether (50 c.c.) was added during 30 minutes to a well stirred solution of ethylmagnesium bromide (prepared from

* [Added, June 27th, 1949.] Two recent papers (Schtschukina and Rubtsov, *J. Gen. Chem. Russia*, 1948, **18**, 1645, Preobrazhenskii and Rubtsov, *ibid.*, p. 1719), received since the present communication was submitted, have also described the conversion of acetylenic ethoxy-carbinols into aldehydes and acids.

2·3 g. of magnesium) in ether (100 c.c.), and the mixture was heated under reflux for 2½ hours during which the complex separated as an oil. After the mixture had been cooled, acetone (5 g.) in ether (50 c.c.) was added dropwise during 30 minutes; the mixture was heated under reflux for 1½ hours and then cooled to 0°. The complex was decomposed by addition of ammonium chloride (20 g.) in water (100 c.c.), and the product isolated in the usual manner with ether, giving 1-*ethoxy*-3-*methylbut*-1-*yn*-3-*ol* (6·7 g.) as a mobile liquid, b. p. 72°/11 mm., n_D^{20} 1·4420 (Found: C, 65·25; H, 9·35. $C_7H_{12}O_2$ requires C, 65·6; H, 9·4%).

β-Methylcrotonaldehyde (VII; R = Me).—The above carbinol (0·9 g.) in ethyl acetate (20 c.c.) was shaken in an atmosphere of hydrogen in the presence of a palladium–calcium carbonate catalyst (0·1 g.; 2% Pd) until 168 c.c. (20°/777 mm.) had been absorbed (equivalent to 1 double bond). After removal of the catalyst and evaporation of the solvent under reduced pressure, the residue was dissolved in methanol and treated with methanolic 2 : 4-dinitrophenylhydrazine sulphate. The resulting precipitate was crystallised from alcohol, giving dark red needles (1·0 g.), m. p. 179°, undepressed on admixture with an authentic specimen of the 2 : 4-dinitrophenylhydrazone of β-methylcrotonaldehyde (Braude and Jones, *J.*, 1945, 498, give m. p. 179°).

β-Methylcrotonic acid (VIII; R = Me).—1-Ethoxy-3-methylbut-1-yn-3-ol (1·2 g.) was shaken with 10% (w/v) sulphuric acid (10 c.c.) for 3 minutes. The ester thus formed was isolated by means of ether and hydrolysed by heating under reflux for 3 hours with a solution of potassium hydroxide (2 g.) in methanol (15 c.c.). After cooling, the solution was diluted with water (100 c.c.), and the non-hydrolysable material extracted with ether. The aqueous solution was then acidified with 10% (w/v) sulphuric acid and distilled. The first 100 c.c. of distillate were collected and extracted thoroughly with ether. Drying and evaporation of the ethereal solution gave β-methylcrotonic acid (0·5 g.) which crystallised from water in needles, m. p. 68°, undepressed on admixture with an authentic specimen (Ives, Linstead, and Riley, *J.*, 1933, 561, give m. p. 70°).

1-*Ethoxy*-3-*methylpent*-4-*en*-1-*yn*-3-*ol* (V; R = CH_2:CH).—A solution of methyl vinyl ketone (7·0 g.) in ether (50 c.c.) was added at 0° during 30 minutes to a well stirred suspension of ethoxyacetylenylmagnesium bromide (prepared from 2·3 g. of magnesium and 7·3 g. of ethoxyacetylene) in ether (200 c.c.), and the mixture was heated under reflux for 1½ hours. After the mixture had been cooled to 0°, the complex was decomposed by addition of ammonium chloride (20 g.) in water (100 c.c.), and the product isolated with ether in the usual way. Distillation, accompanied by some decomposition, gave 1-*ethoxy*-3-*methylpent*-4-*en*-1-*yn*-3-*ol* (4·3 g.), b. p. 54—55°/0·1 mm., n_D^{20} 1·4590 (Found: C, 68·2; H, 8·8. $C_8H_{12}O_2$ requires C, 68·55; H, 8·65%).

1-*Ethoxy*-3-*methylpenta*-1 : 4-*dien*-3-*ol and* 3-*Methylpenta*-2 : 4-*dien*-1-*al*.—The above carbinol (3·1 g.) in ethyl acetate (25 c.c.) was shaken in an atmosphere of hydrogen in the presence of a palladium–calcium carbonate catalyst (0·5 g.; 2% Pd) until 525 c.c. (20°/765 mm.) had been absorbed (equivalent to 1 double bond). The reaction was then interrupted, the catalyst and solvent were removed, and the residue was distilled, giving 1-*ethoxy*-3-*methylpenta*-1 : 4-*dien*-3-*ol* (2 g.), b. p. 35°/0·1 mm., n_D^{24} 1·4530 (Found: C, 68·05; H, 9·85. $C_8H_{14}O_2$ requires C, 67·6; H, 9·9%). When a small portion of the carbinol was shaken with 5% (w/v) hydrochloric acid for 5 minutes, a pungent liquid was obtained. Treatment of the latter with 2 : 4-dinitrophenylhydrazine sulphate in methanol gave the 2 : 4-dinitrophenylhydrazone of 3-methylpenta-2 : 4-dien-1-al which crystallised from ethyl acetate as deep-red needles, m. p. 130—131°, undepressed on admixture with a specimen prepared by the method of Heilbron, Jones, and Julia (this vol., p. 1430). Treatment of the crude aldehyde with a solution of semicarbazide acetate in methanol gave a *semicarbazone* which crystallised from ethyl acetate in needles, m. p. 180—182° (Found: N, 27·6. $C_7H_{11}ON_3$ requires N, 27·45%). Light absorption of the semicarbazone: Maximum, 2810 A.; ε, 27,000. Inflexion, 2950 A.; ε, 22,000. This derivative is isomeric with that, m. p. 166—167° (light absorption: Maximum 2940 A.; ε, 38,000), previously described for 3-methylpenta-2 : 4-dien-1-al (*idem, loc. cit.*).

2-*Methylbuta*-1 : 3-*diene*-1-*carboxylic Acid* (VIII; R = CH_2:CH).—(*a*) Methyl vinyl ketone (6 g.) was condensed with ethoxyacetylenylmagnesium bromide (prepared from 2·3 g. of magnesium and 7 g. of ethoxyacetylene) in the manner described above. After the Grignard complex had been decomposed, the crude ethoxyacetylenic carbinol was extracted with ether, and the ethereal solution (200 c.c.) shaken with 10% (w/v) sulphuric acid (100 c.c.) for 10 minutes, heat being evolved in the process. After cooling to 20°, the ethereal layer was separated, washed well with water, dried, and evaporated. Distillation of the residue gave *ethyl* 2-*methylbuta*-1 : 3-*diene*-1-*carboxylate* (6 g.) with a slightly pungent smell, b. p. 74°/15 mm., n_D^{22} 1·4799 (Found: C, 68·55; H, 8·85. $C_8H_{12}O_2$ requires C, 68·55; H, 8·65%). Light absorption: Maximum 2510 A.; ε, 20,000.

The ester (3·3 g.) was dissolved in a solution of potassium hydroxide (10 g.) in methanol (100 c.c.) and set aside at 20° for 48 hours. Water (200 c.c.) was then added, the non-hydrolysable material extracted with ether, and the aqueous layer acidified with 10% (w/v) sulphuric acid. The liberated acid was isolated by means of ether, giving 2-*methylbuta*-1 : 3-*diene*-1-*carboxylic acid* (1·8 g.), b. p. 60°/0·05 mm., n_D^{23} 1·5186, which crystallised in needles when kept at 0° (Found: C, 63·95; H, 7·4. $C_6H_8O_2$ requires C, 64·15; H, 7·2%). Light absorption: Maximum, 2490 A.; ε, 20,500 (cf. light absorption in hexane of sorbic acid: Maximum 2610 A.; ε, 50,000; Hausser *et al.*, *Z. physikal. Chem.*, 1935, *B*, **29**, 371). The S-*benzylthiuronium* salt crystallised from aqueous alcohol (50%) in needles, m. p. 162° (Found: N, 10·15. $C_{14}H_{18}O_2N_2S$ requires N, 10·0%).

(*b*) A portion (*ca.* 10 c.c.) of a solution of methyl vinyl ketone (9 g.) and ethyl bromoacetate (20 g.) in dry thiophen-free benzene (50 c.c.) was added to activated zinc turnings (8·5 g.), mercuric chloride (*ca.* 0·1 g.), and benzene (100 c.c.), and the mixture was heated under reflux until reaction commenced. The remainder of the ketone–bromoacetate solution was then added dropwise during 30 minutes, and the mixture heated under reflux for a further hour during which most of the zinc dissolved. The liquid was cooled, decanted from unchanged zinc, and shaken with a solution of acetic acid (30 g.) in water (600 c.c.). The benzene layer was washed free from acid, dried, and evaporated. Distillation of the residue gave the crude hydroxy-ester (6·5 g.), b. p. 82°/15 mm., n_D^{23} 1·436.

The crude ester was heated under reflux with anhydrous oxalic acid (15 g.) at 95—100°/15 mm. for

2 hours. After cooling, the residue was extracted with light petroleum (b. p. 60—80°), and the extract washed, dried, and evaporated. Distillation gave the crude dehydrated ester (1·0 g.), b. p. 72—75°/15 mm., n_D^{25} 1·460. Light absorption: Maximum, 2510 A.; $E_{1\,cm.}^{1\%}$, 710. The ester was hydrolysed and the acid (0·8 g.) isolated in the manner described above. It was converted into the *S*-benzylthiuronium salt which crystallised from aqueous alcohol (50%) in needles (0·7 g.), m. p., and mixed m. p. with a specimen from (*a*), 162°.

4-Phenyl-2-methylbuta-1 : 3-diene-1-carboxylic Acid (IX).—A solution of benzylideneacetone (2 g.) in ether (50 c.c.) was added during 15 minutes to a well stirred suspension of ethoxyacetylenylmagnesium bromide (prepared from 1·3 g. of magnesium and 4·5 g. of ethoxyacetylene) in ether (125 c.c.), and the mixture was stirred at 20° for 3 hours. The complex was decomposed by the addition of ammonium chloride (15 g.) in water (75 c.c.). The crude carbinol (2·6 g.), isolated by means of ether, was dissolved in methanol (10 c.c.) containing 1 drop of 10% (w/v) sulphuric acid, and the solution was kept for ½ hour, whereafter 10% (w/v) sulphuric acid (10 c.c.) was added and the product was extracted with ether. Evaporation of the ethereal solution gave a crude ester which was dissolved in a solution of potassium hydroxide (3 g.) in methanol (30 c.c.) and heated under reflux for 2 hours. After cooling, the solution was diluted with water, the non-hydrolysable portion was extracted with ether, and the acid, liberated from the aqueous solution by 10% (w/v) sulphuric acid, was isolated in the usual manner with ether. Crystallisation from light petroleum (b. p. 60—80°) gave 4-phenyl-2-methylbuta-1 : 3-diene-1-carboxylic acid (1·7 g.) as prisms, m. p. 122—124° (Kuhn and Hoffer, *Ber.*, 1932, **65**, 651, give m. p. 123·5—124·5°). Light absorption: Maxima, 2290 and 3090 A.; ε, 13,500 and 28,000, respectively.

β-Ionylideneacetaldehyde and *β-Ionylideneacetic Acid.*—A solution of β-ionone (9·5 g.) (n_D^{18} 1·5200. Light absorption: Maxima 2230 and 2960 A.; ε, 6,500 and 10,000) in ether (50 c.c.) was added dropwise to a well stirred suspension of ethoxyacetylenylmagnesium bromide (prepared from 1·8 g. of magnesium and 5·3 g. of ethoxyacetylene) in ether (50 c.c.), and the mixture was heated under reflux for 2½ hours and then cooled. A solution of ammonium chloride (50 g.) in water (150 c.c.) was added slowly and the product isolated in the usual manner. Distillation gave a pale yellow oil (7·5 g.), b. p. 80—100° (bath temp.)/10^{-4} mm., n_D^{15} 1·5143, exhibiting general absorption in the 2350—2490 A. region ($E_{1\,cm.}^{1\%}$, 300); Maximum, 2960 A.; $E_{1\,cm.}^{1\%}$, 440; inflexion, 3080 A.; $E_{1\,cm.}^{1\%}$, 410.

A portion of the crude carbinol (2·25 g.) in ethyl acetate (40 c.c.) was shaken in an atmosphere of hydrogen in the presence of palladium–calcium carbonate (0·5 g.; 2% Pd) until 80 c.c. (20°/765 mm.) of gas had been absorbed. After removal of the catalyst and evaporation of the solvent, the residue was dissolved in ether (40 c.c.), and the ethereal solution was shaken with 10% (w/v) sulphuric acid for 5 minutes, washed with water, dried, and evaporated. The residue was divided into two equal parts. One was treated with a solution of 2 : 4-dinitrophenylhydrazine sulphate in methanol and gave *β-ionylideneacetaldehyde* 2 : 4-*dinitrophenylhydrazone* (0·4 g.) which crystallised from ethyl acetate in red needles, m. p. 198—200° (Found: N, 14·5. $C_{21}H_{28}O_4N_4$ requires 14·05%). Light absorption (in chloroform): Maxima 2550, 3230, and 4100 A.; ε, 20,500, 15,000, and 42,000, respectively. The second part was treated with a solution of semicarbazide acetate in alcohol and gave β-ionylideneacetaldehyde semicarbazone (0·2 g.) which crystallised from benzene in needles, m. p. 193—195° (Kuhn and Morris, *Ber.*, 1937, **70**, 853, and Arens and van Dorp, *Nature*, 1947, **160**, 189, give m. p. 193—195°). Light absorption: Maximum, 3170 A., ε, 38,000. Inflexion, 3250 A.; ε, 36,000 (Arens and van Dorp, *loc. cit.*, give maximum 3230 A.).

A further portion of the crude carbinol (2 g.) was dissolved in methanol (8 c.c.), containing a few drops of 10% (w/v) sulphuric acid. After 15 minutes the product was isolated by means of ether, and distillation gave crude ethyl β-ionylideneacetate as a pale yellow oil (1·6 g.), b. p. 130—150° (bath temp.)/0·03 mm., $n_D^{15^\circ}$ 1·5342. Light absorption: Maxima, 2230, 3000, and 3150 A.; $E_{1\,cm.}^{1\%}$, 500, 550, and 450, respectively; inflexion, 2650 A.; $E_{1\,cm.}^{1\%}$, 400. The crude ester was dissolved in a solution of potassium hydroxide (2·5 g.) in methanol (20 c.c.), and the mixture was kept at 20° for 24 hours. After dilution with water (100 c.c.) and extraction of the non-hydrolysable portion with ether, the acid, liberated from the aqueous solution by dilute sulphuric acid, was isolated with ether. Trituration of the resulting oil (0·55 g.) with light petroleum (b. p. 40—60°) gave β-ionylideneacetic acid which crystallised from light petroleum (b. p. 60—80°) in needles (0·1 g.), m. p. 124° (Karrer, Salomon, Morf, and Walker, *Helv. Chim. Acta*, 1932, **15**, 878, give m. p. 125°). Light absorption: Maxima, 2600 and 2900—2980 A.; ε, 16,500 and 17,500, respectively (Young, Andrews, and Cristol, *J. Amer. Chem. Soc.*, 1944, **66**, 520, give maxima, 2600 and 2940 A.; ε, 12,900 and 13,700, respectively).

8-cycloHex-1′-enyl-2 : 6-dimethylocta-1 : 3 : 5-trien-7-yne-1-carboxylic Acid (XII).—A solution of 8-*cyclo*hex-1′-enyl-6-methylocta-3 : 5-dien-7-yn-2-one (7 g.) (Heilbron, Jones, and Richardson, this vol., p. 287) in ether (100 c.c.) was added over a period of 45 minutes to a well stirred suspension of ethoxyacetylenylmagnesium bromide (prepared from 3 g. of magnesium and 9·5 g. of ethoxyacetylene), and the mixture was heated under reflux for 1½ hours. After cooling to 0°, the complex was decomposed by the addition of ammonium chloride (50 g.) in water (200 c.c.), and the crude ethoxyacetylenic carbinol (8·6 g.) was isolated in the usual manner with ether. Light absorption: Maximum, 2900 A.; $E_{1\,cm.}^{1\%}$, 510.

This carbinol was dissolved in methanol (50 c.c.), 10% (w/v) sulphuric acid (0·5 c.c) added, and the solution allowed to stand at 20° for 30 minutes. The crude hydroxy-ester, isolated, after dilution with water (100 c.c.), by ether, was heated with anhydrous oxalic acid (35 g.) at 95—100°/0·1 mm. for 3 hours. The residue was extracted with light petroleum (b. p. 60—80°), and the extract was washed with water, dried, and evaporated, giving a crude ester (6·5 g.). Light absorption: Maxima, 3410 and 3480 A.; $E_{1\,cm.}^{1\%}$, 440.

The ester was dissolved in a solution of potassium hydroxide (20 g.) in methanol (200 c.c.) and kept at 20° for 48 hours. Water (500 c.c.) was then added, the non-hydrolysable material extracted with ether, and the aqueous layer acidified to pH 4 with phosphoric acid. The liberated acid was taken up in ether, and the solution was washed and dried. On concentrating the ethereal solution, 8-*cyclo*hex-1′-enyl-2 : 6-dimethylocta-1 : 3 : 5-trien-7-yne-1-carboxylic acid separated and was recrystallised from methanol giving

yellow needles (0·15 g.), m. p. 179—180° (Heilbron, Jones, and Richardson, this vol., p. 287, give m. p. 179° for the "*A* form"). Light absorption: Maxima, 3380 and 2580 A.; ε, 33,000 and 14,000, respectively (*idem, loc. cit.*, give maxima 3390, 2600, and 2570 A.; ε, 27,500, 12,000, and 11,000, respectively).

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391. *Studies in the Polyene Series. Part XXX. The Synthesis of* cyclo*Pentenyl and* cyclo*Heptenyl Analogues of* β*-Ionone.*

By SIR IAN HEILBRON, E. R. H. JONES, J. B. TOOGOOD, and B. C. L. WEEDON.

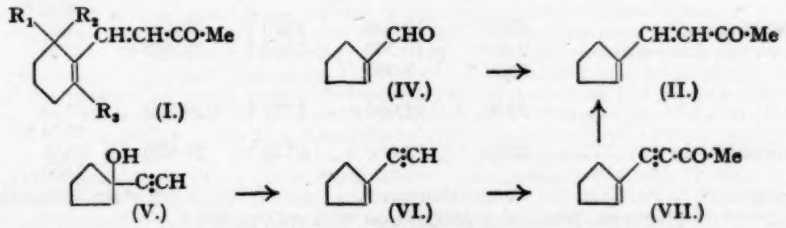
Methods previously developed for the preparation of analogues of β-ionone have now been applied to the synthesis of related compounds possessing *cyclo*pentenyl and *cyclo*heptenyl groups.

The diene ketone (II) was readily obtained by condensation of *cyclo*pentenealdehyde with acetone.

Ethynyl*cyclo*pentene (VI) and ethynyl*cyclo*heptene (IX) were prepared by dehydration of the corresponding acetylene carbinols. Treatment of the ethynyl*cyclo*alkenylmagnesium chlorides with acetic anhydride gave the acetylenic ketones (VII) and (X), which on partial hydrogenation yielded the diene ketones (II) and (III).

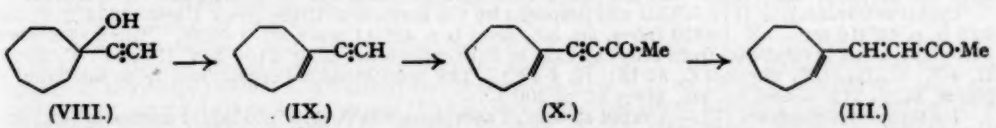
IN Part XXVI of this series (Heilbron, Jones, Richardson, and Sondheimer, this vol., p. 737) attention was drawn to the importance of compounds of the type (I; R_1, R_2, and R_3 = H or Me), both for the preparation of analogues of vitamin A, and also for comparisons with β-ionone, particularly in light-absorption properties and reaction behaviour. As part of the general scheme for the synthesis of compounds with modified β-ionone structures, the *cyclo*pentenyl and *cyclo*heptenyl ketones (II) and (III) have now been prepared by the methods previously developed for the synthesis of the ketone (I; $R_1 = R_2 = R_3 = H$).

4-cyclo*Pent-1'-enylbut-3-en-2-one* (II) was readily obtained in 70% yield by condensation of *cyclo*pentenealdehyde (IV) (Urion, *Ann. Chim.*, **1934**, **1**, 5) with acetone in the presence of sodium hydroxide.



The same ketone was also synthesised by the following route. Vapour-phase dehydration of ethynyl*cyclo*pentanol (V) over aluminium phosphate at 300—310° yielded *ethynyl*cyclo*pentene* (VI) (55%). By condensation of ethynyl*cyclo*pentenylmagnesium chloride with acetic anhydride, the acetylenic *ketone* (VII) was formed (40% yield), and this on partial hydrogenation in the presence of a quinoline-poisoned palladium–charcoal catalyst gave (II), isolated in 20% yield after regeneration from the *semicarbazone*, m. p. 186°.

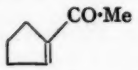
Similarly, *ethynyl*cyclo*heptene* (IX) was prepared (85% yield) from ethynyl*cyclo*heptanol (VIII) and converted into the *ketone* (X) (70% yield). Partial hydrogenation of the latter gave 4-cyclo*hept-1'-enylbut-3-en-2-one* (III) which was obtained in 15% yield after regeneration from the *semicarbazone*, m. p. 183°.



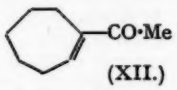
1-Acetyl*cyclo*hexene is obtained conveniently by treatment of 1-ethynyl*cyclo*hexanol with formic acid (cf. Chanley, *J. Amer. Chem. Soc.*, **1948**, **70**, 244). 1-Acetyl*cyclo*pentene (XI) and

1-*acetyl*cyclo*heptene* (XII), required for spectrographic purposes, have now been prepared in a similar manner from the corresponding acetylene carbinols (V) and (VIII).

The light-absorption data for the various compounds described in this paper, together with those of the corresponding *cyclo*hexenyl analogues, are set out in the accompanying Table. The position of maximal absorption of the diene ketones is practically independent of the ring size.



(XI.)



(XII.)

However, in the acetyl*cyclo*alkenes, the *cyclo*pentenyl and *cyclo*heptenyl ketones exhibit maximal absorption at slightly longer wave-lengths than the *cyclo*hexenyl analogue. A similar bathochromic effort is observed in *cyclo*pentenealdehyde as compared with *cyclo*hexenealdehyde.

			2 : 4-Dinitrophenylhydrazone.‡		Semicarbazone.	
	$\lambda_{max.}$, A.	$\varepsilon_{max.}$	$\lambda_{max.}$, A.	$\varepsilon_{max.}$	$\lambda_{max.}$, A.	$\varepsilon_{max.}$
(VI)	2270	10,000	—	—	—	—
Ethynyl*cyclo*hexene	2230	12,500	—	—	—	—
	2280 *	9,500	—	—	—	—
(IX)	2290	11,000	—	—	—	—
(VII)	2760	9,000	3800 †	29,500	2860	17,500
	2700	9,000	—	—	—	—
	2180	7,000	—	—	—	—
4-*cyclo*Hex-1′-enylbut-3-yn-2-one [1]	2720	11,000	3800 †	28,500	2820	16,500
	2220	6,000	—	—	2880 *	15,500
(X)	2800	11,500	3840 †	26,500	2910	17,000
(II)	2810	21,000	3960 †	30,500	2920	38,000
					3020	33,500
(I; $R_1 = R_2 = R_3 = H$) [2]	2810	20,000	3950 †	32,000	2900	35,000
	2730 *	18,500	—	—	3000 *	32,000
(III)	2820	16,500	3970 †	30,000	2930	43,000
	2890 *	15,000	—	—	3040	33,000
(XI)	2390	13,000	3840 †	28,500	2620	25,500
					2650 *	24,500
1-Acetyl*cyclo*hexene	2320	13,000	3870 †	27,500	2600	24,500
(XII)	2360	10,500	3810 †	24,500	2620	27,000
	2400 *	9,000				
(IV)	2370	12,000	3770 †	29,500	2670	30,500
					2770 *	25,500
*cyclo*Hexene-1-aldehyde	2290	12,000	3770 †	28,000	2650	31,500
					2600	28,500

* Inflexion. † In chloroform. ‡ Main band only.

[1] Heilbron, Jones, and Richardson, this vol., p. 287.
[2] Heilbron, Jones, Richardson, and Sondheimer, this vol., p. 737.

Of the acetylenic ketones and ethynyl*cyclo*alkenes, those possessing a *cyclo*heptenyl group show maximal absorption at somewhat longer wave-lengths than either of the smaller ring analogues. In view of the displacements in $\lambda_{max.}$ described above, it is of interest to note that in the case of cyclic unsaturated ketones, those possessing a five-atom ring exhibit maximal absorption at shorter wave-lengths than similar six-atom-ring and acyclic compounds (Gillam and West, *J.*, 1942, 486).

Experimental.

Light-absorption measurements were determined in ethanol, except where stated otherwise, and the data are given in the Table. All the operations were performed in an atmosphere of nitrogen.

cyclo*Pentenealdehyde* (IV).—This was prepared by the method of Urion (*Ann. Chim.* 1934, **1**, 5) and had b. p. 45°/16 mm., n_D^{23} 1·4820 (*idem, loc. cit.*, gives b. p. 48°/11 mm., n_D^{21} 1·4828). The 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl acetate in dark red plates, m. p. 215—216° (Found : C, 52·25; H, 4·3. $C_{18}H_{18}O_4N_4$ requires C, 52·15; H, 4·4%). The semicarbazone crystallised from methanol in plates, m. p. 212° (*idem, loc. cit.*, gives m. p. 209°).

1-*Ethynyl*cyclo*pentanol* (V).—A rapid stream of acetylene was passed into liquid ammonia (4 l.) and sodium (29 g.) was added in small pieces at such a rate that no permanent blue colour developed. A solution of *cyclo*pentanone (105 g.) in ether (500 c.c.) was then added during 1 hour, and the cooled solution stirred overnight. The reaction was terminated by gradual addition of ammonium chloride

(80 g.), the ammonia was allowed to evaporate, and the product was isolated with ether. Distillation gave ethynyl*cyclo*pentanol (87 g.), b. p. 78°/40 mm., which rapidly solidified to needles, m. p. 24° (Backer and van der Bij, *Rec. Trav. chim.*, 1943, **62**, 561, give b. p. 57·5—59°/11 mm., m. p. 21°).

1-*Ethynyl*cyclo*pentene* (VI).—Ethynyl*cyclo*pentanol (50 g.) was slowly distilled (*ca.* 25 g./hour) at 110—120° (bath-temp.)/120 mm. through a Pyrex tube (70 × 2 cm.) maintained at 300—310° and containing a supported aluminium phosphate catalyst (prepared according to Heilbron, Jones, and Richardson, this vol., p. 287). The emergent gases were cooled in air- and water-condensers, and the liquid product was collected in a flask cooled in ice–salt. After the water produced had been separated, the crude material was distilled, and the fraction boiling below 70°/150 mm. was dried ($CaCl_2$) and fractionated to give *ethynyl*cyclo*pentene* (17·8 g.) as a pale yellow mobile liquid with a sharp odour and b. p. 65·5°/125 mm., n_D^{19} 1·4880 (Found: C, 90·9; H, 9·1. C_7H_8 requires C, 91·25; H, 8·8%). By distillation of the high-boiling residue ethynyl*cyclo*pentanol (20 g.), b. p. 76—78°/40 mm., was recovered.

The hydrocarbon (1·168 g. and 1·038 g.) in methyl acetate (5 c.c.) was shaken in hydrogen in the presence of platinic oxide catalyst until absorption ceased. Hydrogen absorbed was 863 c.c. at 17°/764 mm., and 770 c.c. at 19°/765 mm., respectively, equivalent to an average value of 2·9 double bonds.

4-cyclo*Pent*-1′-*enylbut*-3-*yn*-2-*ol*.—Ethynyl*cyclo*pentene (15·3 g.) in ether (40 c.c.) was added dropwise to an ethereal solution of ethylmagnesium bromide (from 4·1 g. of magnesium), and the solution heated under reflux for 1 hour. Acetaldehyde (6·0 g.) in dry ether (40 c.c.) was added and the solution stirred for 1 hour. The complex was decomposed with aqueous ammonium chloride, and the product isolated with ether in the usual manner. Distillation gave 4-cyclo*pent*-1′-*enylbut*-3-*yn*-2-*ol* (16·3 g.), b. p. 50°/0·05 mm., n_D^{18} 1·5200 (Found: C, 79·3; H, 8·9. $C_9H_{12}O$ requires C, 79·35; H, 8·9%). Light absorption: Maximum, 2280 A.; ε, 14,500. Inflexion, 2350 A., ε, 12,500. The 3 : 5-*dinitrobenzoate* crystallised from light petroleum (b. p. 60—80°) in colourless needles, m. p. 127° (Found: N, 8·6. $C_{16}H_{14}O_6N_2$ requires N, 8·5%).

4-cyclo*Pent*-1′-*enylbut*-3-*yn*-2-*one* (VII).—Ethynyl*cyclo*pentene (13 g.) in dry ether (40 c.c.) was added dropwise to an ethereal solution of ethylmagnesium chloride (from 3·5 g. of magnesium), and the mixture heated under reflux for ½ hour. After standing for ½ hour, the cold ethereal suspension of the Grignard reagent was added slowly with stirring to a solution of acetic anhydride (18·0 g.) in ether (100 c.c.) at −60°. Stirring was continued while the temperature of the mixture was allowed to rise to 10° during 7 hours, whereafter ice was added. The etherea llayer was then washed free from acid and dried. Distillation gave 4-cyclo*pent*-1′-*enylbut*-3-*yn*-2-*one* (7·4 g.) as a mildly vesicant liquid, b. p. 55°/0·3 mm., n_D^{19} 1·5276 (Found: C, 80·4; H, 8·0. $C_9H_{10}O$ requires C, 80·55; H, 7·55%). The 2 : 4-*dinitrophenylhydrazone* crystallised from alcohol in orange or yellow needles, m. p. 158° (Found: N, 17·5. $C_{15}H_{14}O_4N_4$ requires N, 17·8%). The *semicarbazone* crystallised in needles, m. p. 164°, from alcohol (Found: N, 22·35. $C_{10}H_{13}ON_3$ requires N, 22·0%).

4-cyclo*Pent*-1′-*enylbut*-3-*en*-2-*one* (II).—(*a*) A solution of the above ketone (VII; 5·7 g.) in methyl alcohol (40 c.c.) was shaken with hydrogen in the presence of a 2% palladium–charcoal catalyst (0·6 g.), partly poisoned with quinoline (Isler, Huber, Ronco, and Kofler, *Helv. Chim. Acta*, 1947, **30**, 1911) until 1 molar proportion of hydrogen had been absorbed (1006 c.c. at 18°/778 mm.). After removal of the catalyst and solvent, distillation gave a pleasant-smelling liquid (4·8 g.), b. p. 40—45°/0·01 mm., n_D^{20} 1·5310. Treatment with semicarbazide acetate (from semicarbazide hydrochloride, 5 g.) in methanol (50 c.c.) gave the *semicarbazone* (3·2 g.) which crystallised from alcohol in needles, m. p. 186° (Found: C, 62·1; H, 7·75. $C_{10}H_{15}ON_3$ requires C, 62·1; H, 7·8%). The semicarbazone (3·0 g.) was heated under reflux for 15 minutes with light petroleum (50 c.c.; b. p. 80—100°) and 2N-sulphuric acid (50 c.c.). Isolation of the product as usual gave 4-cyclo*pent*-1′-*enylbut*-3-*en*-2-*one* (1·3 g.) as a pleasant-smelling liquid, b. p. 85—87°/3 mm., n_D^{23} 1·5442, which solidified at 0° (Found: C, 79·2; H, 9·15. $C_9H_{12}O$ requires C, 79·35; H, 8·9%). The 2 : 4-*dinitrophenylhydrazone* crystallised from acetic acid in dark red prisms, m. p. 215° (Found: C, 56·8; H, 5·1. $C_{15}H_{16}O_4N_4$ requires C, 56·95; H, 5·1%).

(*b*) *cyclo*Pentenealdehyde (7·3 g.) in acetone (15 c.c.) was added slowly with stirring to a solution of sodium hydroxide (1·0 g.) in water (30 c.c.) and acetone (120 c.c.) maintained at 0°. After stirring for 1 hour at 0°, the solution was allowed to warm to 20° during 1·5 hours, poured into water (500 c.c.) and acidified. Isolation of the product with ether gave (i) recovered *cyclo*pentenealdehyde (4·0 g.) and (ii) 4-*cyclo*pent-1′-enylbut-3-en-2-one (3·3 g.), b. p. 44°/0·01 mm., n_D^{23} 1·5432. The 2 : 4-dinitrophenylhydrazone crystallised from acetic acid in dark red prisms, m. p., and mixed m. p. with sample from (*a*), 215°. The semicarbazone crystallised in needles from alcohol, m. p., and mixed m. p. with sample from (*a*), 186°.

1-*Ethynyl*cyclo*heptanol* (VIII).—A solution of sodium acetylide (from 46 g. of sodium) in liquid ammonia (1·5 l.) was prepared by the procedure of Heilbron, Jones, and Weedon (*J.*, 1945, 81). A solution of *cyclo*heptanone (214 g.) in dry ether (400 c.c.) was then added during 1·5 hours, and stirring and cooling were continued for a further 4 hours. The reaction was terminated by the gradual addition of ammonium chloride (110 g.), the ammonia allowed to evaporate, and the product isolated with ether. Distillation gave (i) recovered ketone (70 g.) and (ii) 1-ethynyl*cyclo*heptanol (118 g.), m. p. 14°, b. p. 90°/13 mm., n_D^{22} 1·4880 (Backer and van der Bij, *loc. cit.*, give b. p. 90—92°/12 mm., m. p. 13·5—14°) (Found: C, 77·8; H, 10·65. Calc. for $C_9H_{14}O$: C, 78·2; H, 10·2%). The 3 : 5-*dinitrobenzoate* crystallised from light petroleum (b. p. 60—80°) in needles, m. p. 108—109° (Found: N, 8·85. $C_{16}H_{18}O_6N_2$ requires N, 8·45%).

1-*Ethynyl*cyclo*heptene* (IX).—1-Ethynyl*cyclo*heptanol (40 g.) was slowly distilled at 100—110° (bath-temp.)/18 mm. under the conditions described above for (VI). After the water produced had been separated, the crude product was distilled and the fraction of b. p. <80°/35 mm. was dried ($CaCl_2$) and fractionated, giving 1-*ethynyl*cyclo*heptene* (18·3 g.) as a colourless liquid having a sharp odour and b. p. 78°/35 mm., n_D^{20} 1·4980 (Found: C, 89·55; H, 9·95. C_9H_{12} requires C, 89·9; H, 10·1%). By distillation of the high-boiling residue, ethynyl*cyclo*heptanol (15 g.), b. p. 90—92°/15 mm., was recovered.

The hydrocarbon (0·710 g. and 1·035 g.) in methyl acetate (5 c.c.) was shaken in hydrogen in the

presence of platinic oxide catalyst until absorption ceased. Hydrogen absorbed at 17° and 764 mm. was 416 c.c. and 605 c.c., respectively, equivalent to an average value of 2·97 double bonds.

4-cyclo*Hept*-1′-*enylbut*-3-*yn*-2-*one* (X).—1-Ethynyl*cyclo*heptene (25 g.) in ether (50 c.c.) was added dropwise to an ethereal solution of ethylmagnesium chloride (from 5·1 g. of magnesium), and the mixture was heated under reflux for 2 hours. After cooling, the ethereal suspension of the Grignard reagent was slowly added with stirring to a solution of acetic anhydride (21 g.) in dry ether (100 c.c.) at −60°. After the mixture had been stirred at −60° for 1 hour, the temperature was allowed to rise to 20° during 2 hours. The complex was then decomposed with ice, the ether layer separated, washed free from acid, and dried. Distillation gave (i) recovered ethynyl*cyclo*heptene (5·5 g.) and (ii) 4-(cyclo*hept*-1′-*enyl*)*but*-3-*yn*-2-*one* (18·2 g.), b. p. 65°/0·01 mm., n_D^{21} 1·5280 (Found: C, 81·1; H, 8·8. $C_{11}H_{14}O$ requires C, 81·4; H, 8·7%). The 2 : 4-*dinitrophenylhydrazone* crystallised from alcohol in orange needles, m. p. 142° (Found: N, 16·2. $C_{17}H_{18}O_4N_4$ requires N, 16·35%). The *semicarbazone* crystallised from aqueous alcohol in needles, m. p. 163° (Found: N, 19·1. $C_{12}H_{17}ON_3$ requires N, 19·15%).

4-(cyclo*Hept*-1′-*enyl*)*but*-3-*en*-2-*one* (III).—A solution of the above ketone (X) (13·6 g.) in methanol (50 c.c.) was shaken with hydrogen in the presence of 2% palladium–charcoal (1·3 g.) partly poisoned with quinoline (Isler, Huber, Ronco, and Kofler, *loc. cit.*) until 1995 c.c. of hydrogen had been absorbed at 18°/768 mm. (1 molar proportion). After removal of the catalyst and solvent, the product was distilled. The fraction, b. p. 65—70°/10^{-2} mm., n_D^{22} 1·5280, was treated with semicarbazide acetate (from semicarbazide hydrochloride, 9·0 g.) in methanol (50 c.c.) and gave the *semicarbazone* (3·2 g.) which crystallised from alcohol in needles, m. p. 183° (Found: N, 18·7. $C_{12}H_{19}ON_3$ requires N, 19·0%). The semicarbazone was heated under reflux with vigorous stirring for 15 minutes with light petroleum (50 c.c.; b. p. 80—100°) and 2N-sulphuric acid (50 c.c.). Isolation of the product as usual gave 4-cyclo*hept*-1′-*enylbut*-3-*en*-2-*one* (1·7 g.) as a pleasant-smelling liquid, b. p. 76—77°/0·1 mm., n_D^{24} 1·5400 (Found: C, 80·0; H, 9·95. $C_{11}H_{16}O$ requires C, 80·4; H, 9·8%). The 2 : 4-*dinitrophenylhydrazone* crystallised from acetic acid as red prisms, m. p. 188° (Found: N, 16·5. $C_{17}H_{20}O_4N_4$ requires N, 16·3%).

4-cyclo*Heptylbutan*-2-*one*.—A solution of the ketone (X) (1·3 g.) in methyl acetate (10 c.c.) was shaken with hydrogen in the presence of platinic oxide until absorption ceased. Hydrogen absorbed at 15° and 722 mm. was 585 c.c., equivalent to 3·0 double bonds. Removal of the catalyst and solvent, and distillation of the residue, gave 4-cyclo*heptylbutan*-2-*one* (1·15 g.) as a pleasant-smelling liquid, b. p. 57°/0·1 mm., n_D^{20} 1·4685 (Found: C, 78·1; H, 11·7. $C_{11}H_{20}O$ requires C, 78·5; H, 12·0%). The *semicarbazone* crystallised from aqueous alcohol in plates, m. p. 182° (Found: C, 64·05; H, 10·45. $C_{12}H_{23}ON_3$ requires C, 63·95; H, 10·2%).

1-*Acetyl*cyclo*pentene* (XI).—A solution of 1-ethynyl*cyclo*pentanol (6·0 g.) in 90% formic acid (60 c.c.) was heated under reflux for 2½ hours. The mixture was poured into 2N-sodium carbonate solution (600 c.c.), and the product was isolated with ether. Distillation gave 1-acetyl*cyclo*pentene (3·0 g.), b. p. 67°/16 mm., n_D^{22} 1·4780. Treatment with semicarbazide acetate (from semicarbazide hydrochloride, 3 g.) in methanol (25 c.c.) gave the semicarbazone (3·55 g.) which crystallised from alcohol in needles, m. p. 211—212° (Rapson and Robinson, *J.*, 1935, 1285, give m. p. 210—211°). The semicarbazone (3·3 g.) was heated under reflux for 15 minutes with light petroleum (50 c.c.; b. p. 60—80°) and 2N-sulphuric acid (50 c.c.). Isolation of the product as usual gave 1-acetyl*cyclo*pentene (1·75 g.), b. p. 69°/17 mm., n_D^{23} 1·4776 (*idem*, *loc. cit.*, give b. p. 75—78°/22 mm.). The 2 : 4-*dinitrophenylhydrazone* crystallised from alcohol in bright red needles, m. p. 203° (Found: C, 54·1; H, 5·0. $C_{12}H_{14}O_4N_4$ requires C, 53·8; H, 4·9%).

1-*Acetyl*cyclo*heptene* (XII).—A solution of 1-ethynyl*cyclo*heptanol (5·3 g.) in 90% formic acid (50 c.c.) was heated under reflux for 2½ hours. The mixture was poured into 2N-sodium carbonate solution (600 c.c.), and the product isolated with ether. Distillation yielded the ketone (2·5 g.), b. p. 90—97°/17 mm., n_D^{23} 1·4878, which gave no colour with Schiff's reagent. Treatment with semicarbazide acetate (from semicarbazide hydrochloride, 3 g.) in methanol (30 c.c.) gave the *semicarbazone* (2·8 g.) which crystallised from alcohol in needles, m. p. 197° (Found: C, 61·65; H, 8·4. $C_{10}H_{17}ON_3$ requires C, 61·5; H, 8·75%). The semicarbazone (1·6 g.) was heated under reflux for 15 minutes with light petroleum (40 c.c.; b. p. 60—80°) and 2N-sulphuric acid (40 c.c.). Isolation of the product as usual gave 1-*acetyl*cyclo*heptene* (0·9 g.), b. p. 97°/16 mm., n_D^{25} 1·4900 (Found: C, 78·05; H, 10·0. $C_9H_{14}O$ requires C, 78·2; H, 10·2%). The 2 : 4-*dinitrophenylhydrazone* crystallised from alcohol in crimson plates, m. p. 178° (Found: C, 56·3; H, 5·4. $C_{15}H_{18}O_4N_4$ requires C, 56·6; H, 5·15%).

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392. *The Mechanism of Inhibition of Corrosion of Iron by Chromic Acid and Potassium Chromate.*

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An examination has been made of the mechanism by which the corrosion of iron is inhibited by aërated solutions of chromic acid and potassium chromate. The view is put forward that the iron ions are oxidised, while still in the solid lattice, to γ-ferric oxide, which forms a thin continuous film on the iron. This film is impervious to iron ions, and thus corrosion is prevented.

The work described in this paper was designed to elucidate the mechanism by which aërated solutions of chromic acid and potassium chromate inhibit the corrosion of iron. Previous theories relating to inhibition by solutions of potassium chromate can be divided into three classes :

(1) The precipitation theory. Hoar and Evans (*J.*, 1932, 2476) examined the protective mechanism of potassium chromate solutions and concluded that inhibition was due to the plugging of weak points in the primary air-formed film by a mixture of hydrated ferric and chromic oxides (cf. Evans, " Corrosion Handbook," p. 9, 1948, John Wiley & Sons).

(2) The adsorption theory. Uhlig (*Chem. Eng. News*, 1946, 3154) put forward the view that inhibition by solutions of chromates was brought about by the adsorption of a unimolecular layer of chromate ions, in such a manner that they satisfied the secondary valency forces of the iron ions without disrupting the metal lattice.

(3) The oxide-film theory. Evans (*J.*, 1927, 1020; *Trans. Amer. Inst. Min. Met. Eng.*, 1929, 7) isolated the film from a freshly abraded iron specimen, which had been immersed in potassium chromate solution. He stated that " the main function of the chromate, in the case of electrolytic iron, is clearly to repair the discontinuities in the oxide film, which had already commenced to grow during the grinding in the air, but, in addition, there is some evidence that the chromate causes thickening of the film." Furthermore he showed that the film was not appreciably attacked by 0·1N-hydrochloric acid and concluded that it consisted of anhydrous ferric oxide as distinct from the hydrated product. His conclusion was supported by the electron-diffraction studies of Iitaka, Miyake, and Iimori (*Nature*, 1937, **39**, 156), which showed that the stripped film was composed of either γ-Fe_2O_3 or Fe_3O_4.

Both Evans and Iitaka *et al.*, however, passivated iron surfaces carrying a film of air-formed oxide, which has been shown to consist of γ-Fe_2O_3 (Iitaka, Miyake, and Iimori, *loc. cit.*; Nelson, *J. Chem. Physics*, 1937, **5**, 252; Vernon, *Trans. Faraday Soc.*, 1935, **31**, 1677). The films stripped from such passive specimens would consist of a mixture of the original air-formed oxide with any film produced by the chromate, and so it is not easy, from these experiments, to determine the exact function of the chromate. In the present work the action of chromates on oxide-free surfaces was investigated, to obtain further information on the part played by chromic acid and potassium chromate solutions during inhibition.

Experimental.

Materials.—The iron used in the film-stripping experiments was sheet 0·2 mm. thick. It was kindly supplied by the British Iron and Steel Research Association and had the following analysis : C, 0·005; Si, 0·0075; S, 0·013; P, 0·003; Mn, 0·007; Ni, 0·018; Cr, 0·02; Cu, 0·003; O, 0·12; N, 0·008; H, 0·00009%. Each specimen, measuring 4 × 1·5 cm., was degreased with xylene, abraded with 3/0 emery, swabbed with acetone, and dried, immediately before each experiment. In some experiments, discs 2 cm. in diameter and 1 mm. thick were required. These were cut from iron sheet of the same composition. The faces for examination were abraded, under alcohol, down to 4/0 emery and finally polished with magnesia on selvyt cloth, except when otherwise stated. The surfaces were then most carefully degreased in redistilled benzene and finally ethyl alcohol.

Pure chromic acid and AnalaR potassium chromate were used.

Passivation of the Specimens.—The specimens were immersed in 60 ml. of 0·2N-hydrochloric acid for 15 seconds, in order to remove the air-formed oxide film; the acid was then rapidly displaced upward by a large volume (1 l.) of the passivating solution. The operation was carried out in a glass tube, the bottom of which had been drawn down and sealed to a glass tap. A small side tube was sealed in near the top of the vessel to allow the excess of solution to run to waste. A large reservoir containing the chromate was connected to the bottom of this vessel by a rubber tube. The rate of flow of the chromate could be adjusted by altering the relative heights of the tube and reservoir. After the acid had been completely displaced, the tap at the bottom of the tube was closed and the specimen left in contact with the solution for the required period. During displacement of the hydrochloric acid by potassium chromate some chromic acid will be formed; the chromic acid will, however, be in contact with the metal only for a very short time and, since film formation is not instantaneous, this effect has been neglected. After this treatment the specimen was removed from the solution, washed rapidly in distilled water, and dried on filter paper.

Electron-diffraction Examination by the Reflection Method.—Specimens in the form of discs were passivated in M-chromic acid for 2 days and 0·1M-potassium chromate for six days by the method previously described. Further specimens, which had not been passivated, were immersed in 0·1N-hydrochloric acid for 10 seconds, washed carefully in distilled water, degreased in redistilled benzene, and allowed to grow air-formed oxide films for different times in a desiccator. The nature of the surface of these specimens was then examined by electron-diffraction, using the reflection method.

The type of pattern obtained from specimens carrying an air-formed film depended, not only on the time of exposure to air, but also on the abrasive pretreatment of the surface, as pointed out by Jackson and Quarrell (2nd Rep. of Alloy Steels Research Committee, I.S.I., 1939, **24**, 65). A specimen that had been abraded down to 3/0 emery, etched for 10 seconds in 0·1N-hydrochloric acid and exposed to dry air for 15 minutes, showed only an α-iron pattern when its surface was examined by reflection (Table I).

TABLE I.

Ring radius, R (cm.).	Spacing, *d* (A.).	Intensity.	*hkl*.	Lattice parameter, A.
0·73	2·05	S	110	2·90
1·02	1·43	M	200	2·86
1·28	1·15	S	211	2·82
1·62	0·905	M	310	2·86
1·94	0·755	M	321	2·83
2·15	0·68	W	330	2·88
				Mean: 2·86 ± 0·04 A.

S = strong; M = moderate; W = weak.

TABLE II.

Ring radius, R (cm.).	Spacing, *d* (A.).	Intensity.	*hkl*.	Lattice parameter, A.
0·84	3·38	S	211	8·28
1·17	2·45	S	311	8·12
1·48	1·92	S	331	8·36
1·74	1·62	W	511, 333	8·41
1·94	1·47	S	440	8·31
2·14	1·22	S	444	8·44
2·67	1·04	W	800	8·32
				Mean: 8·28 ± 0·16 A.

TABLE III.

Ring radius, R (cm.).	Spacing, *d* (A.).	Intensity.	*hkl*.	Lattice parameter, A.
0·87	4·2	W	200	8·4
1·49	2·5	S	311	8·29
2·35	1·5	S	440	8·46
3·02	1·2	W	444	8·30
				Mean: 8·38 ± 0·08 A.

The lattice parameter was found to be 2·86 ± 0·04 A., gold-leaf being used for calibration; this is in good agreement with the *X*-ray value of 2·86 A. previously determined by Hull (*Phys. Review*, 1917, **10**, 661).

A specimen that had been abraded down to 4/0 emery, etched for 10 seconds in 0·1N-hydrochloric acid, and exposed to dry air for 30 minutes gave a more diffuse iron pattern, together with two broad oxide haloes, at spacings of approx. 2·5 and 1·5 A., when its surface was examined by reflection (cf. Nelson, *loc. cit.*). Exposure of a similarly treated specimen to dry air for 48 hours gave a series of sharp rings characteristic of either γ-Fe_2O_3 or Fe_3O_4. In this case no iron rings could be detected.

A specimen that had been passivated in M-chromic acid for 2 days, when examined by the reflection method, gave a ring pattern in reasonable accord with that of γ-Fe_2O_3 or magnetite. In this case the rings obtained were quite sharp, and there was no evidence of reflection from the underlying iron. The results are recorded in Table II.

The mean value of the lattice parameter was found, using gold-leaf for calibration, to be 8·28 ± 0·16 A.

The specimen that had been passivated for six days in 0·1M-potassium chromate solution gave a series of diffuse haloes when its surface was examined by reflection. As in the case of the specimen passivated in chromic acid, there was no evidence of reflection from the underlying iron. The calculated values of the spacings were in reasonable accord with either γ-Fe_2O_3 or Fe_3O_4. The results are shown in Table III.

The calculated value of the lattice parameter was found, using gold-leaf as calibration, to be 8·38 ± 0·08 A., in fair agreement with the values found in the previous experiments.

Isolation of the Film.—The films on the passivated specimens were stripped from the metal by the method of Vernon, Wormwell, and Nurse (*J.*, 1939, 621), except that the solutions were moved through the apparatus by means of a partial vacuum. Each specimen was treated with a solution of iodine in dry methyl alcohol, in an atmosphere of nitrogen; after 30—90 minutes, the solution was removed and the specimen washed with dry methyl alcohol. The specimen was then transferred to a dish of dry alcohol, and the film detached by gentle agitation.

Several of the larger pieces of film were floated on to fine copper gauzes and examined by electron diffraction. The remaining portions, which were feebly magnetic, were examined by chemical tests.

Chemical Examination of the Film Substance.—Portions of the film were suspended in M-chromic acid, and 0·1N- and 2N-hydrochloric acid. There was no evidence of attack, when the film was examined under the microscope, after 4 days' treatment with M-chromic acid or with 0·1N-hydrochloric acid, whereas samples of ferric and chromic hydroxide, both in the freshly precipitated and aged (1 week) condition, dissolved in a few minutes in either reagent. The hydroxides were prepared by shaking solutions of ferrous salts and potassium chromate, and those of ferric, ferrous, and chromium salts with sodium hydroxide or ammonium hydroxide. At a magnification of 500, attack on the film substance could just be detected after 24 hours' treatment with 2N-hydrochloric acid; samples of rust, however, prepared by partly immersing steel specimens in distilled water, tap water, or sea-water, were dissolved by this treatment.

A portion of the film, obtained by passivation in potassium chromate solution, was dissolved in 5N-hydrochloric acid; the solution was found to be free from ferrous ions when tested with di-2-pyridyl. The total iron was then determined colorimetrically with thioglycollic acid, and from these results and the known sensitivity of the di-2-dipyridyl test it was estimated that the film substance contained less than 2·5% of ferrous iron. Magnetite, when tested in a similar manner, gave a positive reaction with di-2-pyridyl, even after 2 hours' contact with an alcoholic solution of iodine.

Electron-diffraction Examination of Stripped Films by Transmission.—The film stripped from iron passivated for 2 days in M-chromic acid showed a well-defined ring structure characteristic of either γ-Fe_2O_3 or Fe_3O_4. The calculated values of the spacings are shown in Table IV.

TABLE IV.

Ring diameter, D (cm.).	Spacing, *d* (A.).	Intensity.	*hkl.*	Lattice parameter (A.).
1·58	4·18	W	200	8·36
2·26	2·92	M	220	8·26
2·63	2·51	VS	311	8·32
2·98	2·22	M	321	8·31
3·19	2·07	S	400	8·28
3·87	1·705	W	422	8·35
4·14	1·59	M	511, 333	8·27
4·52	1·46	S	440	8·26
5·28	1·25	W	622	8·29
6·35	1·04	W	800	8·32
7·92	0·835	VW	933	8·31
			Mean:	8·30 ± 0·06 A.

VS = very strong; VW = very weak; cf. also Table I.

The mean value of the lattice parameter was found, using gold-leaf as a standard, to be 8·30 ± 0·06 A., in good agreement with the previously determined value of 8·30 A. (Wyckoff, "Structure of Crystals," 1931, p. 267, American Catalog Co., Inc.) for γ-Fe_2O_3. Furthermore there was considerable evidence of a preferred orientation in the film. All the rings obtained were characteristic of the γ-Fe_2O_3 structure, and there was no evidence of the presence of a second phase. There was, however, a certain incoherent scattering of electrons which resulted in a lessening of contrast around the central spot.

The film stripped from iron passivated for two days in M-potassium chromate gave only diffuse oxide haloes when examined by transmission. A specimen was, therefore, passivated in 0·01M-potassium chromate solution for 14 days, and the film stripped from it. This film, when examined by transmission, gave an extremely good ring pattern characteristic of either γ-Fe_2O_3 or Fe_3O_4. The values of the spacings are shown in Table V.

TABLE V.

Ring diameter, D (cm.).	Spacing, *d* (A.).	Intensity.	*hkl.*	Lattice parameter (A.).
2·13	2·93	M	220	8·29
2·48	2·51	VS	311	8·32
2·99	2·085	S	400	8·34
3·24	1·92	W	331	8·36
3·64	1·71	W	422	8·36
3·89	1·60	M	511, 333	8·31
4·23	1·47	S	440	8·32
4·87	1·28	W	533	8·38
5·10	1·21	W	444	8·38
5·68	1·11	W	642	8·30
			Mean:	8·34 ± 0·04 A.

The mean value of the lattice parameter was found, using gold-leaf for calibration, to be 8·34 ± 0·04 A., which agrees well with that found in the previous experiment with chromic acid (8·30 ± 0·06). Incoherent scattering of the electrons was again observed, but there were no rings that indicated the presence of a second phase.

DISCUSSION.

An iron specimen, abraded down to 4/0 emery and exposed to dry air for 30 minutes, gave an α-iron pattern together with two diffuse oxide haloes. According to Miley and Evans (*J.*, 1937,

1295), the mean thickness of the air-formed oxide film, after 30 minutes' air exposure, is 160 A. If, however, the oxide film was allowed to grow in air for 48 hours, after which time its thickness will be about 200 A. (Miley and Evans, *loc. cit.*), the pattern obtained by reflection was characteristic of either γ-Fe_2O_3 or magnetite. The film formed by passivation in either chromic acid or potassium chromate solution gave rings that fitted approximately with either the γ-Fe_2O_3 or the Fe_3O_4 structure. With the specimen passivated in chromic acid an anomalous reflection was observed from the (211) plane. This is a forbidden reflection for the face-centred cubic spinel type of structure, and is characteristic of a lower form of symmetry. This line has previously been observed by Iimori (*Sci. Papers Inst. Phys. Chem. Res., Tokyo*, 1937, **34**, 60), using *X*-rays, and also by Haul and Schoon (*Z. physikal. Chem.*, 1939, *B*, **44**, 216), and thus probably is a true function of the oxide structure and not merely due to the relaxing of the third Laue condition during electron diffraction, as pointed out by Jackson and Quarrell (*loc. cit.*). As no iron rings were observed, the film formed during passivation is clearly thicker, or more continuous, than the oxide film formed by 30 minutes' air exposure; it cannot, therefore, consist of a unimolecular layer of chromate ions, which is claimed by Uhlig to be responsible for passivity. Internal stresses in the film could arise from the fact, originally pointed out by Pilling and Bedworth (*J. Inst. Metals*, 1923, **29**, 529), that an increase in volume accompanies the conversion of iron into oxide. It is probable that it is these internal stresses which are directly responsible for the fact that the patterns obtained by reflection are characteristic of the distorted γ-Fe_2O_3 or Fe_3O_4 structure.

The stress relief that undoubtedly accompanies film stripping leads to the production of very good ring patterns by transmission, possibly by allowing recrystallization of the film substance. The film stripped from specimens passivated in chromic acid or dilute potassium chromate solution gave well-defined ring patterns which were in excellent accord with either the γ-Fe_2O_3 or the Fe_3O_4 structure. All the rings, except one, marked permissible reflections for either structure. It was clearly brought out, in the case of specimens passivated in chromic acid, that reflection from the (321) plane was occurring. This is an impossible reflection for the face-centred cubic spinel type of structure and is characteristic of a lower form of symmetry—probably either the primitive or body-centred cube. This reflection has previously been observed from γ-Fe_2O_3, by use of *X*-rays (Bannister, " Index of *X*-Ray Diffraction Constants," A.S.T.M., 1945, Haul and Schoon, *loc. cit.*), but never from magnetite. Goldschmidt (*J. Iron and Steel Inst.*, 1942, **146**, 157P) has pointed out the close crystallographic resemblance between α-iron, ferrous oxide, and magnetite, and has indicted how these two oxides can be built up from the α-iron lattice with a minimum of rearrangement of the iron atoms. Magnetite, which has the face-centred cubic spinel structure, contains 24 iron (16 ferric and 8 ferrous) and 32 oxygen atoms per unit cell. According to Verwey (*J. Chem. Physics*, 1935, **3**, 593), γ-Fe_2O_3 has a practically identical structure with 32 oxygen atoms and, on the average, only 21·3 iron (ferric) atoms in the unit cell. The γ-Fe_2O_3 lattice, therefore, contains more vacant sites than that of magnetite and might be expected, in some circumstances, to show evidence of a lower form of symmetry. There is, however, additional evidence to support the view that the film is largely composed of γ-Fe_2O_3 and not Fe_3O_4. The chemical examination of the film substance indicated that it contained less than 2·5% of ferrous ions. Furthermore, the stripped film was only feebly magnetic. These points, taken in conjunction with the electron-diffraction data, make it probable that the film formed during passivation in solutions of chromic acid or potassium chromate, is largely composed of γ-Fe_2O_3.

The transmission photographs of the stripped films all indicate the presence of a certain amount of incoherent scattering of the electron beam, which results in a decrease in contrast around the central spot. This may imply that a certain amount of the film substance is without characteristic interatomic distance, possibly owing to some residual internal stress. Furthermore, as some of the stripped films show a marked preferred orientation, probably inherited from the underlying metal, which was in the rolled condition, it is probable that the film is built as a continuation of the α-iron lattice, and not merely laid on the metal.

It is now considered by the authors that the objection, previously raised, that film stripping may alter the constitution of the surface layer (Jackson and Quarrell, *loc. cit.*), is no longer valid. It has been demonstrated that the stripped film gives patterns similar to those of the oxide in contact with the metal. The only effect of stripping is probably to allow recrystallisation of the film substance, which produces clearer patterns.

The observations, that the film substance is composed largely of γ-Fe_2O_3, which has been found to be visibly unattacked by 2N-hydrochloric acid, and that precipitated hydrated oxides, produced by a homogeneous reaction in solution, were very readily soluble in this reagent,

indicate that chromate ions must have reacted with the iron ions before they had left the solid lattice; for had the iron ions passed into solution, they would have become hydrated and been precipitated as a hydrated product. Thus inhibition must be considered, not as a homogeneous reaction between two ions in solution, but rather as a heterogeneous reaction between ions in solution and the iron surface. Probably, the first step in the reaction is an adsorption of chromate ions on the iron surface, and this is followed by oxidation of the iron and reduction of the chromate ion. The chromate ion may be destroyed (i) by oxidising the iron directly, (ii) by reduction at cathodic areas on the metal, or (iii) by interaction with hydrogen atoms adsorbed on adjacent cathodic areas, as suggested by Pyke and Cohen (*J. Electrochem. Soc.*, 1948, **93**, 63). Whichever of these mechanisms is correct, the oxide film will thicken, either by migration of iron ions outward or by the crack-heal mechanism suggested by Evans (*Nature*, 1946, **157**, 732) (or both), until it becomes almost impermeable to iron ions. When this state is attained, the iron will have become passive, provided that sufficient inhibitor is present to heal any cracks subsequently produced in the film.

The electron-diffraction examination failed to indicate the presence of any phase except γ-Fe_2O_3. If any chromium compounds are present in the film, they will be there in amounts less than 10%. Clearly this is much less than the stoicheiometric proportion of tervalent chromium formed in the equation $2K_2CrO_4 + 5H_2O + 2Fe = Fe_2O_3 + 4KOH + 2Cr(OH)_3$.

In common with iron and aluminium hydroxide, the first amounts of chromic hydroxide would be expected to form colloidally, and so it is not surprising that tervalent chromium compounds appear in the film only in very small amounts, as shown by Hoar and Evans (*loc. cit.*). Films formed by passivation in M-chromic acid (pH 0·5) probably contain no chromic compounds, as the hydrated tervalent chromic ions would be readily soluble at this pH. In the case of potassium chromate, the chromic hydroxide, formed by the reduction of the chromate ion, may well interfere with the grain growth of the γ-Fe_2O_3 film. The film stripped from a specimen passivated for two days in M-potassium chromate solution gave diffuse rings characteristic of oxide with a very small crystal size. Passivation in 0·01M-potassium chromate for a much longer time (14 days), in which case the film would be expected to grow much more slowly and have a larger grain size, produced a film that gave very clear oxide pattern by transmission.

It should be noted that throughout this investigation no attempt has been made to separate the effect of oxygen in solution from that of the chromate ion. Darrin (*Ind. Eng. Chem.*, 1945, **37**, 741) has shown, however, that chromates can inhibit in the absence of oxygen.

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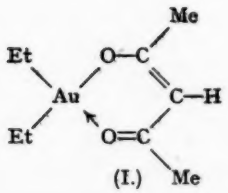
393. *The Organic Compounds of Gold. Part XI. Diethylthiocyanatogold.*

By W. L. G. GENT and C. S. GIBSON.

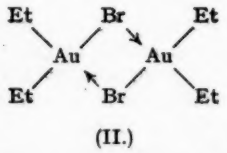
Diethylthiocyanatogold (VI) has been prepared and its properties investigated. The molecule is dimeric, containing a four-membered ring of two gold and two sulphur atoms, and resembles, therefore, the diethylbromogold dimer and not the diethylcyanogold tetramer previously described. The compound is chiefly remarkable for the resistance of the sulphur–gold linkages to the co-ordinating action of nitrogenous bases, no complexes of which could be isolated, but thiourea and thioacetamide both react easily. Thermal decomposition of (VI) in the liquid state and in solution leads to the formation of *aurous thiocyanate*. Some complexes of this compound are described.

THE properties of organic compounds of gold having the formula $(R_2AuX)_n$ (R = alkyl; X = acetylacetone, Br, CN, etc.; n = 1, 2, 4, etc.) and derived co-ordination complexes with ammonia, pyridine, and ethylenediamine have been described by Gibson *et al.* (*J.*, 1930, 2531; 1931, 2407; 1934, 860; 1935, 217, 1024; 1939, 762). As in all auric compounds, the gold atom is 4-covalent and the number of gold atoms in the molecule it would seem, if we compare diethylacetylacetonylgold monomer (I), diethylbromogold dimer (II), and diethylcyanogold

tetramer (III), is determined by the co-ordinating direction of the negative group and the intervalency angle of gold.



(I.)



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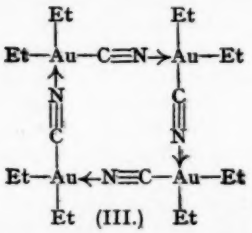
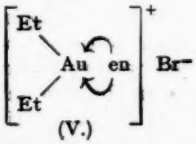


(III.)

The co-ordinate linkages holding the $(R_2AuX)_n$ molecules together are easily replaced by those with ammonia, pyridine, or ethylendiamine, resuling in the formation of covalent and then ionic compounds such as monoethylenediaminotetraethyldibromodigold (IV) and monoethylenediaminodiethylgold bromide (V). A remarkable property of the substances is the low

(IV.)



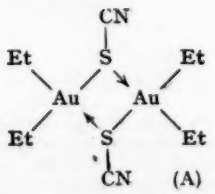
(V.)

temperature (*ca.* 100°) at which alkyl groups are lost as the hydrocarbon R_2, leaving finally the polymeric aurous compound of empirical formula AuX, but often passing through the stage of a definite auroso-auric compound.

The substances $(R_2AuX)_n$ in which X = halogen are generally similar to one another in behaviour and there is little difference between them and that of the cyano-compound. The thiocyanato-group allows linkage of gold to a bivalent sulphur atom which might be expected to impose a more marked effect than the carbon atom of the cyanide group.

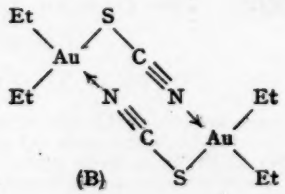
Diethylthiocyanatogold (VI) is readily prepared from the corresponding bromo-compound. It is a colourless, crystalline non-electrolyte, the molecular weight of which in freezing *cyclo*hexane indicates it to be dimeric.

Since the thiocyanato-group is linear, either of the structures (A) or (B) might be proposed. The fact that by the action of ammonia, ethylenediamine, or dipyridyl no derivative could be isolated in a solid or crystalline state is in sharp contrast to the behaviour of the cyano-compound and must be ascribed to the very strong co-ordination affinity between sulphur and gold which cannot be effectively broken by a co-ordinating nitrogen atom. Sulphur compounds, however, such as thiourea form complexes with (VI) fairly readily. The form (A) is preferable so far as chemical evidence is concerned; in dimensions it resembles the structure of diethylbromogold and might be expected to show a greater stability than the eight-membered heterocyclic ring of (B).



(A)

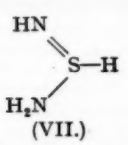
(VI.)



(B)

It followed naturally from the assumption of the sulphur-bridged structure that isolation of complexes with sulphur compounds should be attempted. Dibenzyl sulphide was found to be without action. Whereas the sulphur of the thiocyanate group is of a negative character, that of dibenzyl sulphide is more neutral. On the principle " like displaces like " aqueous sodium sulphide was used and gave rise to a colourless substance insoluble in all common organic solvents. This suggested that the material is polymeric, but the empirical formula could not be determined since, on drying, a black substance of indefinite composition was formed. This had such a high gold content as to imply that a large proportion of the alkyl groups had been lost.

Thiourea is known to contain a proportion of *iso*thiourea (VII) which it was deemed might allow the sulphur atom to be a competitor with that in (VI). *Diethylthioureidothiocyanatogold*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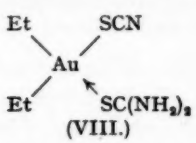
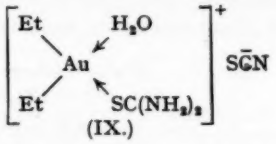
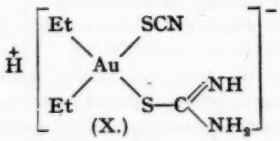

(VIII.)


(IX.)

(VIII) is readily isolated as a stable compound and is unexpectedly somewhat soluble in water (*ca.* 0·5% w/v) to give an acid solution which develops a distinctive red-brown colour, different from that of ferric thiocyanate, with ferric chloride.

Formation of a hydrated complex (IX) is thereby excluded and the simplest assumption is that of an *iso*thiourea *derivative* (X).

The thiourea complex (VIII) was found to be soluble with difficulty in aqueous thiourea solution which, however, gives a reaction for thiocyanate ion indicating that diethyldithioureidogold thiocyanate (XI) is present in solution. From such solutions a picrate and a chromate can be precipitated; the latter compound was not investigated. It was to be expected that the picrate would have a composition (Et_2Au tu_2)pic (tu = thiourea; pic = picrate ion) analogous to (XI) but, in fact, this was associated with an extra molecule of thiourea, *i.e.*, it had the empirical formula Et_2Autu_3pic. The method of purification of the *complex* ruled out the possibility that the extra molecule is contained in the crystal lattice apart from the gold complex, so that the odd thiourea molecule is associated either with the complex cation or with the picrate ion. All evidence points to the former being the point of attachment. The *dithioureidoaurous thiocyanate* (XII), described later, when precipitated with picric acid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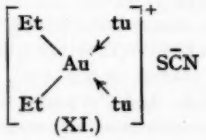
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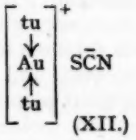
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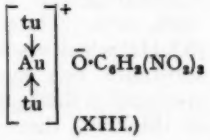
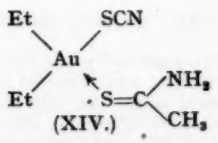

(XIII.)

gave a normal *picrate* (XIII), and Dixon's observation (*J.*, 1917, **111**, 185) that only one complex is formed between thiourea and picric acid was confirmed. This complex is evidently not completely dissociated in water, since it gives a deep red colour with sodium hydroxide, but a saturated solution of the gold complex does not show this reaction until after boiling with dilute acid. Since in aurous compounds the two covalencies are at an angle of 180° to one another (Elliott and Pauling, *J. Amer. Chem. Soc.*, 1938, **60**, 1846), it follows that the association of the extra thiourea molecule must be related to the square configuration of the two ethyl groups and the two co-ordinated thiourea molecules.

Of other sulphur compounds with an enolic disposition, thioacetamide was used to prepare *diethylthioacetamidothiocyanatogold* (XIV), which is soluble in an excess of thioacetamide, the solution showing a reaction for thiocyanate ion due presumably to the formation of diethyldithioacetamidogoldthiocyanate (XV) of which the isolation was not attempted.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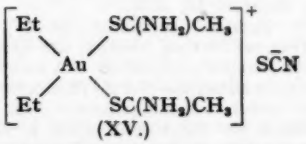

(XV.)

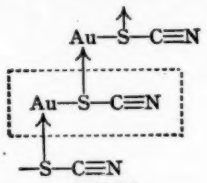
The thermal decomposition of diethylthiocyanatogold differs from that of the corresponding tetrameric cyano-compound in that no substance similar to diethyldicyanodigold was isolated, the products of decomposition being always *aurous thiocyanate* (XVI) and butane. On heating the compound in bulk above 100° aurous thiocyanate is not formed, but gold and an orange polymer of thiocyanogen are produced.

The compound (VI) melts to a clear liquid at 63° and below about 80° there is little decomposition even if the substance is kept at such temperatures for some time. Above 80° there is an induction period, which shortens as the temperature rises, during which butane is evolved at an increasing rate until finally the decomposition becomes explosive. The reaction is clearly not unimolecular and probably involves a chain mechanism. The simplest explanation

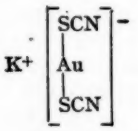
is that thermal activation results in the ejection of an ethyl radical, and to become stable in the aurous state the gold atom releases the other radical of its pair. These may either terminate the chain by combining to form butane or may attack another diethylgold group to remove one ethyl group as butane and release the other as a radical :

$$(Et_2AuSCN)_2 \longrightarrow (Et_2AuSCN)_2^* \longrightarrow Et_2AuSCN,AuSCN + 2Et$$
$$Et + (Et_2AuSCN)_2 \longrightarrow C_4H_{10} + Et_2AuSCN,AuSCN + Et$$
$$Et + Et_2AuSCN,AuSCN \longrightarrow C_4H_{10} + 2AuSCN + Et$$

Diethylthiocyanatogold decomposes in hydrocarbon solvents to give aurous thiocyanate; careful purification of the liquids is necessary to avoid reduction of some of the compound to gold. The preparation of pure aurous thiocyanate (XVI) by decomposition of the parent substance in xylene enabled the preparation of *potassium aurothiocyanate* (XVII) to be made. Like diethylthiocyanatogold, the aurothiocyanate ion is resistant to the attack of co-ordinating agents. Both dipyridyl and pyridine are without action on this ion and no evidence was



(XVI.)



(XVII.)

(XVIII.)

obtained of 4-covalent aurous compounds such as were isolated from the action of dipyridyl and *o*-phenanthroline on potassium aurocyanide (Dothie, Llewellyn, Wardlaw, and Welch, *J.*, 1939, 426). Thiourea, however, gives an immediate precipitate of *thioureidothiocyanatogold* (XVIII) which is soluble in thiourea solution to give dithioureidoaurous thiocyanate (XII). This substance was easily isolated and is a stable compound. From its solution picric acid precipitates dithioureidoaurous picrate (XIII), and the same substance is precipitated in excess of thiourea, there being no molecular association as with the corresponding diethylgold compound.

Experimental.

Diethylthiocyanatogold (VI).—Silver thiocyanate was prepared by double decomposition of silver nitrate and potassium thiocyanate.

Preliminary experiments were carried out in acetone to prepare diethylthiocyanatogold, but it was found that ligroin (b. p. 40—60°) caused less reduction to metallic gold. A five-fold molecular excess of silver thiocyanate was used, the concentration of diethylbromogold being about M/150. Upon adding the silver salt there appeared to be almost immediate formation of silver bromide. The mixture was shaken for 3 hours, filtered, and the residue extracted twice with ligroin. The solution was then evaporated under reduced pressure and the compound appeared in the form of colourless needle-shaped crystals (90% of theoretical yield). Without further purification the compound is stable for some months when stored in the absence of light.

The gold content of *diethylthiocyanatogold* was found by direct ignition (Found : Au, 62·7. $C_5H_{10}NSAu$ requires Au, 63·0%). The compound is readily soluble in *cyclo*hexane, and the molecular weight was determined by depression of the freezing point of this substance (Found : *M*, 628, 618. $C_{10}H_{20}N_2S_2Au_2$ requires *M*, 626).

A carefully purified specimen of (VI) had m. p. 62—64° without decomposition. The changes occurring on further heating are described below.

Reaction with nitrogen compounds. A solution of the parent compound (0·5 g.) in ligroin (10 ml.) was treated with ethylenediamine (0·1 g.) in alcohol (5 ml.). No precipitation was observed, and the solution was evaporated under reduced pressure over concentrated sulphuric acid. An oily residue remained which crystallised on treatment with a small quantity of methyl alcohol. The crystals after purification by solution in ligroin and evaporation (0·4 g.) had m. p. 59°, not depressed by admixture with the parent compound. Evidently, no compound is formed with ethylenediamine under these conditions. A similar experiment with an aqueous solution of ethylenediamine also gave a negative result.

Equimolecular amounts of the parent substance and pyridine dissolved in ligroin precipitated a small quantity of an oil. A portion of this oil on treatment with methyl alcohol crystallised, the solid being found to be (VI) as before. The main bulk of the solution was evaporated under reduced pressure over concentrated sulphuric acid. Small needle-shaped crystals appeared, but disappeared after a short time, leaving oily drops. On standing overnight these again crystallised, the residue being the parent compound.

Similar experiments with ammonia, dipyridyl, and quinoline gave negative results.

Reaction with dibenzyl sulphide. Equimolecular amounts of the parent substance and dibenzyl sulphide were dissolved in ligroin, and the solution evaporated under reduced pressure. A crystalline

non-homogeneous mass remained. It was extracted with ethyl alcohol and this solution evaporated. The solid recovered was shown to be dibenzyl sulphide, 95% of that used being recovered.

Reaction with sodium sulphide. The parent substance (0·2 g.) was dissolved in ligroin and treated with a five-fold excess of sodium sulphide (0·1 g.). A creamy precipitate was formed on shaking; this was separated and extracted twice with ligroin. The combined volumes of ligroin contained no gold nor did the aqueous layer, but this showed a strong thiocyanate-ion reaction. The solid is extremely water-repellent and insoluble in any of the common solvents. On drying in a vacuum, it changed to a black powder (Found: Au, 83·3%).

Thioureidodiethylthiocyanatogold (VIII).—Equimolecular proportions of diethylthiocyanatogold and thiourea were dissolved in ligroin and water, respectively, and mixed. On shaking, a white precipitate formed which was separated and dried. Recrystallisation from acetone failed, the compound being too highly soluble. Dilution of acetone solutions with either water or ligroin precipitated the *compound* in a pure state. Alternatively, it was crystallised from chloroform to give small colourless needles having m. p. 88° (Found: Au, 50·7. $C_6H_{14}N_2S_2Au$ requires Au, 50·6%).

Saturated aqueous solutions of (VIII) or filtrates from the purification process of precipitation from acetone showed a characteristic red-brown coloration on treatment with ferric alum solution. On treatment with a few drops of mineral acid the colour of ferric thiocyanate appeared. Furthermore, these solutions were found to be acidic. A small quantity of the complex dissolved in acetone (2 ml.) and precipitated by water showed a pH of *ca.* 4·5. A control experiment indicated a pH of 5·5. A similar effect was shown by a saturated aqueous solution. The amount dissolved was about 0·05%.

Diethyldithioureidogold Thiocyanate (XI).—When the parent substance and thiourea in a molecular ratio of 1 : 2 were dissolved in ligroin and water respectively, and shaken together, a quantity of diethylthioureidothiocyanatogold was precipitated, the aqueous layer showing an intense thiocyanate ion reaction. On increasing the ratio of thiourea to (VI) to 3 and 4 : 1, the precipitation was not completely inhibited. It was assumed that the ionic complex might be isolated if the anion were changed, but clearly, silver or barium salts of the common anions could not be used since both of these metals would remove thiourea from the solution also. Picric acid and potassium chromate were used, both giving yellow precipitates.

Diethyldithioureidogold Picrate–Thiourea.—A solution of diethylthioureidothiocyanatogold in a ten-fold molecular excess of thiourea dissolved in water was precipitated by adding an excess of picric acid in aqueous solution. The precipitate was separated and dried. It was highly soluble only in acetone and in ethanol. Evaporation of these solutions gave only powdery residues; dilution with water or ligroin yielded small canary-yellow needles, decomposing at 214° (Found: Au, 27·7; C, 21·8; H, 3·37; S, 13·5; N, 17·6. $C_{13}H_{24}N_8O_7S_2Au$ requires Au, 27·7; C, 21·9; H, 3·37; S, 13·5; N, 17·8%). The *complex* was not sufficiently soluble in any suitable solvent to allow determination of molecular weight.

A saturated solution of the compound in water showed no change in colour on addition of a drop of sodium hydroxide, but after boiling with a drop of dilute hydrochloric acid followed by addition of sodium hydroxide a deep golden-yellow colour was developed.

Picric Acid–Thiourea Complex.—Equimolecular amounts of picric acid and thiourea were dissolved in hot glacial acetic acid. On cooling, the solution was diluted with ligroin, and a bright yellow precipitate appeared. After purification, this compound had m. p. 125—127° and is clearly the same substance as that prepared by Dixon (*loc. cit.*). Similar experiments with 2 and 3 molecular proportions of thiourea yielded mixtures of the compound and thiourea, so only one molecular complex is formed.

It was reported by Dixon that the complex breaks up in aqueous solution, but on dissolving equimolecular amounts of the complex and picric acid in equal volumes of water and adding an equal volume of sodium hydroxide to each, the picric acid solution precipitated its sodium salt whilst the solution of the complex showed a deep red coloration. Addition of more thiourea to this solution caused no further colour change, indicating that only the 1 : 1 molecular ratio is significant and that an equilibrium between complex and components is not involved.

Diethylthioacetamidothiocyanatogold (XIV).—The parent substance (0·2 g.) and thioacetamide (0·05 g.), dissolved in ligroin and water respectively, precipitated a colourless *compound* on being shaken together (Found: Au, 50·5. $C_7H_{15}N_2S_2Au$ requires Au, 50·7%). This compound was soluble in excess of thioacetamide, thiocyanate ion being detected in an aqueous solution, but the ionic complex could not be isolated.

Thermal Decomposition of Diethylthiocyanatogold.—On rapidly heating a specimen of (VI) in an ignition tube, decomposition takes place explosively, gold being left and an orange substance condensing in the cool parts of the tube. This appeared to be a polymer of thiocyanogen. More gentle heating in a melting-point apparatus indicated that decomposition begins at about 80° increasing until at 110° visible outgassing takes place. By 120° this had ceased and a colourless compound remained which at 140° decomposed, leaving gold and the orange compound.

For studying the decomposition quantitatively a modified Victor Meyer's apparatus was constructed, the decomposition tube of which was immersed in a thermostatically controlled oil-bath. The gaseous product of the reaction is butane as the following experiments show: (*a*) The compound (0·2813 g.), heated at 100°, decomposed explosively after 2 minutes. Volume of gas at N.T.P., 19·8 ml. Expected volume, 20·2 ml. (calculated as butane). (*b*) The compound (0·1547 g.), heated at 89·3°, decomposed explosively after 7 minutes. Volume of gas at N.T.P., 11·0 ml. Expected volume, 11·1 ml. (calculated as butane).

An attempt was made to follow the rate of evolution of butane, the results being shown in graphical form in the figure for temperatures of 89·3° and 79·8° respectively.

On rapidly heating a solution of diethylthiocyanatogold in xylene or toluene to its boiling point a colourless precipitate was formed. This substance is aurous thiocyanate (see below). Decomposition in benzene and tetralin gave the same product. All of these solvents needed careful purification, otherwise reduction of the compound to metallic gold took place to a greater or lesser extent.

The time elapsing before appearance of aurous thiocyanate does not seem to depend on the solvent; *e.g.*, at 80°, benzene, toluene, and xylene all deposited the colourless thiocyanate after about 12 minutes

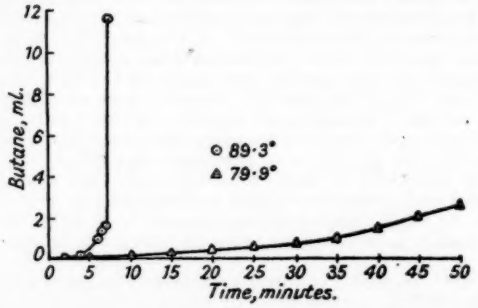
at similar concentrations. The time before precipitation depends very markedly, however, on the temperature of the solvent as the following data indicate:

Temp.	80°	107°	114°	129°
Time, secs.	720	25	17	10

Aurous Thiocyanate (XVI).—Diethylthiocyanatogold (2 g.) was added in small portions with continual stirring to 100 ml. of carefully purified xylene kept at about 125° in an oil-bath. After a few seconds aurous thiocyanate is precipitated as a white flock. Usually there is a faint tinge of blue due to minute traces of colloidal gold. The suspension was allowed to stand for 5 minutes to allow the decomposition to reach completion, and then filtered off, and washed first with xylene and then with acetone. After drying in a vacuum, the *aurous thiocyanate* was a colourless powder insoluble in any solvent (Found: Au, 77·1. AuSCN requires Au, 77·3%). The compound decomposes at about 140° into metallic gold and a thiocyanogen polymer.

Potassium Aurothiocyanate (XVII).—Attempts to prepare this substance by addition of aurous thiocyanate to aqueous solutions of potassium thiocyanate failed. Although the aurous thiocyanate is freely soluble, the complex is unstable in aqueous solution and rapidly deposits gold.

A saturated solution of potassium thiocyanate was prepared in absolute alcohol, and aurous thiocyanate added with shaking until an excess was apparent. The solution was shaken for some time longer and then filtered and evaporated under reduced pressure. Potassium aurothiocyanate appeared in small, colourless, non-hygroscopic needles which show no signs of decomposition when kept dry during several months.



The compound was analysed by dissolving it in water, and rapidly adding a molecular proportion of thiourea to precipitate the gold as the thiourea–thiocyanate complex. This was separated, and the filtrate and washings titrated with standard silver nitrate [Found: KSCN, 27·4. $KAu(SCN)_2$ requires KSCN, 27·6%].

On dissolving the compound in water, a cloudy solution is formed which increases with dilution, indicating an equilibrium between the complex and its components.

Thioureidothiocyanatogold (XVIII).—Thiourea (0·048 g.) was added to an aqueous solution of potassium aurothiocyanate (0·223 g.). The new *complex* was precipitated as a heavy colourless powder; it was purified by dissolving the crude dried material in acetone and diluting with ligroin. Although it was soluble in both acetone and alcohol, neither of these solutions yielded crystalline material. The compound decomposes sharply at 132° (Found: Au, 59·2. $C_3H_4N_3S_2Au$ requires Au, 59·5%).

Dithioureidoaurous Thiocyanate (XII).—Thioureidothiocyanatogold was treated with one molecular proportion of thiourea in 1% aqueous solution in which the whole completely dissolved. On evaporation under reduced pressure small colourless needles appeared. These were dissolved in alcohol, and the *compound* precipitated by dilution with ligroin (Found: C, 9·05; H, 1·90; Au, 48·2. $C_3H_8N_6S_3Au$ requires C, 8·84; H, 1·97; Au, 48·4%).

In some preparations the initial evaporation of the aqueous solution yielded crystals in about equal proportions of needles and hexahedral platelets. Hand separation of these showed that both had the same m. p., 125—126°. Potassium aurothiocyanate was found to have no reaction with pyridine or with 2 : 2′-dipyridyl. On recrystallisation from water both forms yielded needles.

Dithioureidoaurous Picrate.—A solution of (XII) in water yielded a voluminous precipitate with picric acid. This was separated, dried, and recrystallised from acetone in which it is moderately soluble. This *picrate* crystallised in masses of long golden-yellow needles decomposing at 215° (Found: Au, 33·8. $C_8H_{10}N_7O_7S_2Au$ requires Au, 34·1%).

Precipitation of (XII) in the presence of a five-fold molecular excess of thiourea by picric acid yielded the same picrate.

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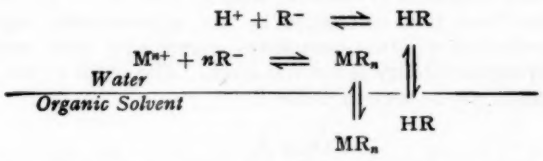
394. *Metal Complexes and Partition Equilibria.*

By H. Irving and R. J. P. Williams.

Many metals form inner complexes which can be extracted from aqueous solution on shaking with an immiscible organic solvent. The extractability is now shown to vary with the hydrogen-ion concentration of the aqueous phase and the concentration of excess reagent, and to depend upon the valency of the metal ion and the partition coefficients and dissociation constants of the various molecular species involved. An explicit relationship between the percentage of metal extracted and the pH of the aqueous phase is derived in terms of $pH_{\frac{1}{2}}$, the hydrogen-ion exponent at which the extraction reaches 50%: this is itself a function of the excess of reagent present. The effect of a change of solvent on the rate of attaining partition equilibrium and on the percentage of metal then extracted, and the consequences of competitive complex formation in the aqueous phase, are discussed in relation to contemporary analytical procedures.

The interaction of an n-valent kation M^{n+} with an organic reagent HR often yields an inner complex MR_n which is sparingly soluble in water though relatively soluble in non-polar solvents. When therefore an aqueous solution of M^{n+} is shaken up with a solution of the reagent HR in a solvent immiscible with water, the equilibria depicted in Fig. 1 come into play and some of the

Fig. 1.



complex formed in accordance with equation (1) will partition into the aqueous phase. Such partition equilibria are involved in many analytical procedures in constant use (*e.g.*, the extrac-

$$M^{n+} + nHR \rightleftharpoons MR_n + nH^+ \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

tion and absorptiometric determination of trace metals with dithizone and oxine, the fluorometric determination of gallium, etc.; cf. Sandell, " The Colorimetric Determination of Traces of Metals "). An appreciation of the difficulties in determining mercury with dithizone in the presence of copper (Irving, Andrew, and Risdon, this vol., p. 541) and a consideration of the principles underlying the valuable procedures of extractive titration, together with problems encountered in the separation of related kations (as metal complexes) by counter-current extraction or partition chromatography, emphasised the need for a generally applicable and quantitative treatment of such partition equilibria. The present paper contains a simple theoretical treatment by which it is possible to relate the percentage of a metal extracted to the concentration of reagent, the pH of the aqueous phase, and the dissociation constants and partition coefficients of the various molecular species involved. It is intended as a general introduction to a series of experimental studies of specific systems which will be published in due course.

Quantitative Treatment of Partition Equilibria.—Consider first the case of a reagent HR which behaves as a monobasic acid throughout the range of pH studied. It is postulated that this reagent and its metal complex MR_n exist in both water and the organic solvent as unassociated molecules. Relevant equilibrium constants are defined as follows:

The instability constant of the complex,

$$K_c = [M^{n+}]_w[R^-]_w^n/[MR_n]_w \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

The Brønsted dissociation constant of the reagent,

$$K_r = \{H^+\}_w[R^-]_w/[HR]_w \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

Partition coefficients,

$$p_c = [MR_n]_w/[MR_n]_o \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

and

$$p_r = [HR]_w/[HR]_o \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

where the subscripts c and r refer to the complex and reagent, and the subscripts w and o refer to the aqueous and the organic phase respectively; K_c is, of course, the reciprocal of the " gross " complexity constant of the complex MR_n as defined by Bjerrum (" Metal Ammine Formation

in Aqueous Solution," Copenhagen, 1941, p. 54). The ratio of the amount of metal extracted as complex into the organic phase to that remaining in all forms in the aqueous phase is termed the (true) extractability, E_t, and is given by

$$E_t = [MR_n]_o/\{[MR_n]_w + [M^{n+}]_w\} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

$$= 1/\{p_e + ([M^{n+}]_w/[MR_n]_o)\}$$

$$= 1/\{p_e + (p_e K_r \{H^+\}_w^n / p_r^n K_r^n [HR]_o^n)\}$$

$$= 1/\{p_e + (\{H^+\}_w^n / K[HR]_o^n)\} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

from equations (2), (3), (4), and (5), whereby

$$K = (K_r p_r)^n / K_e p_e \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

If the partition coefficient p_e of the metal complex is negligible in comparison with the numerical value of the second term in the denominator of equation (7), this reduces to

$$E = K([HR]_o/\{H\}_w)^n \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

Kolthoff and Sandell (*J. Amer. Chem. Soc.*, 1941, **63**, 1906), discussing the extraction of zinc by dithizone, arrived at an expression of this form by assuming that the concentration of complex in the aqueous phase, $[MR_n]_w$, was always negligible when compared with that of the ion, $[M^{n+}]_w$; but this may not be justifiable in general when the extraction of metal is nearly completed. It follows from equations (7) and (9) that $E_t = E/(1 + p_e E)$, so the true extractability will always be less than that calculated by the approximate expression (9). Since, however, the partition coefficient of inner complexes is generally very small, the discrepancy is negligible so long as the extractability is not too large. The order of magnitude of the error for various values of p_e and E can be seen in Table I.

TABLE I.

Percentage of extraction is assumed to be:	E.	Actual percentage of extraction calculated for: $p_e = 0{\cdot}1$.	$p_e = 0{\cdot}01$.	$p_e = 0{\cdot}001$.
100	∞	90·9	99·0	99·9
99	99	90·1	98·0	98·9
90	9	82·6	89·2	89·9
50	1	47·6	49·75	49·8

Whilst equation (9) shows how a change in hydrogen-ion concentration would affect the relative amounts of metal in the two phases, an explicit relationship between the percentage of metal extracted and the pH of the aqueous phase would be of more immediate practical value. Writing equation (9) in the equivalent logarithmic form

$$\log_{10} E = \log_{10} K + n(\mathrm{pH} + \log_{10} [HR]_o) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

and defining $pH_{\frac{1}{2}}$ as that value of the hydrogen-ion exponent when *for the same concentration of excess reagent* the extraction reaches 50% ($E = 1$), we have

$$0 = \log_{10} 1 = \log_{10} K + n(pH_{\frac{1}{2}} + \log_{10} [HR]_o) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

Subtracting, we have

$$n\Delta\mathrm{pH} = n(pH_{\frac{1}{2}} - \mathrm{pH}) = -\log_{10} E \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (12)$$

$$= \log_{10} (100 - x)/x$$

where x is the percentage of metal extracted into the organic phase. Now equation (12) presents pH as a function of x, and we require the inverse function. By an obvious transformation the desired equation is

$$x = 50(1 - \tanh 1.1513\, n\Delta\mathrm{pH}) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (13)$$

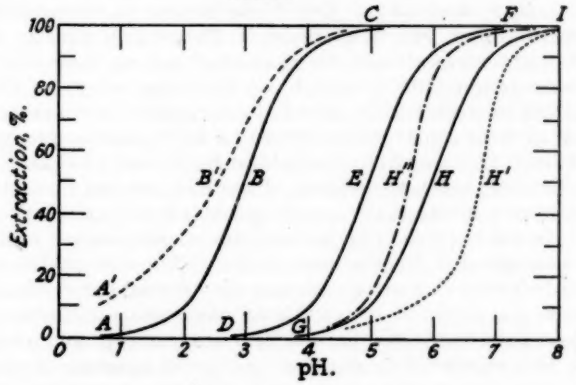
which is shown plotted in Fig. 2 (curve *ABC*) for the particular case of a bivalent metal ($n = 2$) where $pH_{\frac{1}{2}} = 3{\cdot}0$. Values of 0% and 100% extraction are approached asymptotically, whilst the whole curve is centrosymmetric with respect to B ($pH_{\frac{1}{2}}$, 50%), it being assumed that p_e for this system is negligible (see above). From equation (9), and assuming that the concentration of excess reagent amounted to 10^{-5} g.-mol./l., we calculate the value of the extractability constant K for this particular metal–reagent–solvent system to be 10^4. Curves *DEF* and *GHI* are plotted for the same system for values of $pH_{\frac{1}{2}}$ equal to 5·0 and 6·0, corresponding to concentrations of excess reagent of 10^{-7} and 10^{-8} respectively. It will be noted that they are identical in form and that they could be obtained from *ABC* by a simple lateral translation equal to the change in $pH_{\frac{1}{2}}$ value.

The Effect of Changes in Hydrogen-ion and Reagent Concentration.—From Fig. 2, or more directly from equation (10) whence by differentiation

$$(\partial \log E/\partial \mathrm{pH})_{[\mathrm{HR}]_o} = (\partial \log E/\partial \log [\mathrm{HR}]_o)_{\mathrm{pH}}$$

it is clear that a change in extractability due to an increase (or decrease) of one unit in pH can be exactly offset only by a ten-fold decrease (or increase) in the concentration of excess reagent in the organic phase. Now purely practical considerations often limit the permissible variations in the magnitude of the latter parameter. The upper limit is set by the solubility of the reagent—and this is often quite small—whilst in cases where the metal complex is to be determined absorptiometrically a large excess of reagent would be undesirable if it had an appreciable extinction coefficient at the wave-length used for measurements. It is precisely this feature which complicates the use of dithizone in such procedures. On the other hand, where more than one extractable complex can be formed from a metal and an organic reagent (a specific example is provided by copper and dithizone) an adequate excess of reagent is imperative to ensure the stoicheiometric or constant composition of the material extracted. Furthermore, the amount of reagent naturally plays a significant rôle in the kinetics of complex formation (see p. 1845), and its concentration must not be diminished too greatly if complex formation and partition equilibrium are to be effected in a reasonable time. Since such varied factors can and must restrict the possible variations in the term $[\mathrm{HR}]_o$, it is clear that changes in hydrogen-ion

FIG. 2.



concentration (which may readily be varied by a factor of 10^{14}) are of overwhelming importance in the practical applications of partition equilibria.

It should be emphasised that the term $[\mathrm{HR}]_o$ refers explicitly to the *excess* of reagent present in the organic phase at equilibrium. This may differ but little from the total amount of reagent employed if the amount of metal to be extracted is relatively small, or where the pH of the aqueous phase is such that the percentage extracted is negligible; but even in circumstances where the amount of complex formation is strictly limited, the term $[\mathrm{HR}]_o$ may comprise but a small fraction of the total concentration of reagent should the pH of the aqueous phase and the value p_r of the partition coefficient of the reagent be such as to cause a large proportion of it to be extracted into the aqueous phase. The extent to which this can take place in the case of a typical organic reagent, dithizone, is described in the following paper and its consequences in analytical procedures are discussed elsewhere (Irving, Risdon, and Andrew, this vol., p. 537). The difficulty of determining the actual value of $[\mathrm{HR}]_o$ is perhaps the greatest single obstacle in testing the applicability of the foregoing equations to specific systems.

The Influence of the Valency of the Metal Ion.—By differentiating equation (13), the slope of the extraction curve is found to be given by

$$\mathrm{d}x/\mathrm{d}\ \mathrm{pH} = 57{\cdot}57n(1 - \tanh^2 1{\cdot}1513n\Delta\mathrm{pH})$$

which is a function of n, the number of protons liberated when the metal complex is formed. At its mid-point ($x = 50\%$, $\Delta\mathrm{pH} = 0$) its numerical value is $57{\cdot}57n\%$ per pH unit, a prediction which has been verified in the case of zinc and dithizone (Irving and Williams, unpublished). It follows from equation (9) that an increase of one unit in the pH will increase the extractability ten-fold in the case of a univalent metal, but 100-fold and 1000-fold in the case of bi- and ter-

valent metals respectively. The position of the extraction curve with respect to the origin will likewise be subject to greater displacement owing to a change in the amount of uncombined reagent as the valency of the metal ion increases. An appreciation of such factors is obviously of great importance when studying the extraction of mixtures of metals of different valency, *e.g.*, the determination by dithizone of lead and bismuth in admixtures.

The Extraction of Different Metals with the Same Reagent.—We are now in a position to discuss problems arising out of the extraction of a series of metals by a solution of the same organic reagent in a given solvent. In considering the probable values of the individual extractability constants, K, for such systems we note that, of the various factors into which such constants can be resolved by equation (8), K_r and p_r refer to the reagent–solvent system and do not vary, whilst the magnitudes of the partition coefficients p_c, p_c', p_c'' . . . for the various metal complexes are likely to be of much the same order. Most of the variation is to be expected in the values of K_c, K_c', K_c'' . . ., the instability constants of the respective metal complexes. These constants are related by equation (11) to the $pH_{\frac{1}{2}}$ values which serve to characterise the partition equilibria. The more stable the complex, the more acid will be the medium from which it can be completely extracted. That such variations in K_c are of decisive importance is confirmed at least for compounds of the bivalent ions of the transition metals with dithizone by the fact that the sequence of $pH_{\frac{1}{2}}$ values is identical with their " natural " order of stabilities which has been shown to be independent of the nature of the ligand—whether ammonia, ethylene- or propylene-diamine, salicylaldehyde, glycine, quinaldinic acid, etc. (Irving and Williams, *Nature*, 1948, **162**, 746).

The curves *ABC*, *DEF*, and *GHI* of Fig. 2 were drawn to represent a system with $K = 10^4$ and $[HR]_o = 10^{-5}$, 10^{-7}, and 10^{-8}, respectively. They could equally well represent systems with $K = 10^6$, 10^2, and 1, respectively, for the extraction of three different (bivalent) metals by a constant concentration (10^{-6} g.-mol./l.) of the same reagent. Clearly, a knowledge of the mutual disposition of such curves (or of the necessary parameters $pH_{\frac{1}{2}}$ or K, and $[HR]_o$ which would permit of their construction) would be an invaluable prerequisite to any reasoned attempt at separation. This was first pointed out by Wichman (*Ind. Eng. Chem. Anal.*, 1939, **11**, 66), who sketched the probable relative disposition of the extraction curves for various metal–dithizone systems from the many qualitative and semi-quantitative observations reported in the literature. He did not take into account the displacements which would be caused by variations in the amount of dithizone used in the different experiments. Many subsequent workers have published series of curves relating the percentage of metal extracted to the pH of the aqueous phase for partition systems involving metals and oxine, dithizone, and other reagents. They need not be specified here as they are unacceptable for quantitative treatment for one or both of two reasons. In the first place, the amount of excess reagent is seldom specified. Indeed, it is not often a constant amount for any given curve, for it is common practice to obtain such curves by measuring the percentage of extraction obtained when a solution of organic reagent of constant initial concentration is shaken with a fixed amount of metal dissolved in aqueous buffers of varying pH. Clearly, as the percentage of metal extracted is diminished by reducing the pH below that required for complete extraction, the excess of reagent in the organic layer must increase. There results a distorted curve (*e.g.*, *A'B'C* of Fig. 2) which lies to the left of the theoretical curve *ABC* and approximates to it the more closely the higher the pH. The second reason for rejecting most published data is that they do not represent systems at equilibrium.

Equilibrium Conditions.—When describing the routine details of the extraction stage preliminary to specific absorptiometric determinations, analysts have—with few exceptions—been at pains to specify carefully the minimum time (or minimum " number of shakes ") needed to ensure complete extraction at that optimum pH where it had been found that this was effectively quantitative. The assumption commonly made that equilibrium is attained within the same period of time when plotting the course of the extraction curve at lower pH values is quite unjustifiable. Indeed, measurements on the copper–dithizone system by Barnes (*J. Marine Biol. Assoc.*, 1946, **26**, 303; *Analyst*, 1947, **72**, 469) and by Irving, Andrew, and Risdon (*loc. cit.*), and data on other metal–dithizone and metal–oxine systems (Irving *et al.*, to be published) clearly demonstrate that the rate at which the metal complex is formed and extracted into the organic phase decreases rapidly as the pH is reduced below that value appropriate to 100% extraction. Failure to reach true equilibrium will give false extraction curves (*e.g.*, *GH'I* in Fig. 2) lying below the true equilibrium curves plotted for a constant amount of reagent. Furthermore, whilst *CB'A'* may represent true equilibrium conditions in a system with a gradually increasing excess of reagent, a curve closely resembling *CBA* may result if the same system is

studied under conditions where true equilibrium is not reached. The literature provides numerous examples of extraction curves which appear superficially to follow the course predicted by equation (13); but where the excess of reagent may have varied and no true guarantee of equilibrium is provided, such data are useless for the present purpose.

The simple test for the attainment of equilibrium—the approach to a common value from either side—has not apparently been applied to metal–complex partition problems. This is quite understandable, since the analysts who have studied them in greatest detail have been more interested in defining conditions essential to the extraction of a single species or favouring the predominant extraction of one constituent of a mixture. Indeed, failure to reach equilibrium within a given time may be of great practical value. Thus the fact that mercury (but not copper) is rapidly extracted at low pH values by a solution of dithizone in chloroform has been exploited by Barnes and by Irving *et al.* (*locc. cit.*) in methods for the determination of mercury in the presence of copper.

However, in 1942 Walkley (*Proc. Austral. Chem. Inst.*, **9**, 29) observed that the organic phase resulting from shaking a solution of zinc " dithizonate " in chloroform with acid contained a greater percentage of zinc than was obtained by extracting the same quantity of zinc from aqueous solution at the same pH and for the same length of time. The implications of this discovery do not appear to have been generally realised. We have confirmed them and observed similar behaviour in other metal–reagent systems. Whenever a solution of a metal complex in an organic solvent is shaken with an aqueous buffer, reaction with hydrogen ions will cause some decomposition in the sense of equation (1) right to left, and more or less metal ion will pass into the aqueous phase whilst the concentration of reagent in the organic phase will increase until new equilibrium conditions governed by equation (9) are set up. The rate of attaining equilibrium is found to depend on hydrogen-ion concentration and to increase rapidly as the pH is lowered. At sufficiently low acidities (*e.g.*, point *G* of Fig. 2) equilibrium is attained so rapidly that correct values for the percentage of metal extracted at equilibrium are obtained after even a brief period of shaking. At higher pH values (*e.g.*, point *I* of Fig. 2), where the extraction is virtually complete, no significant error will appear in the measured extraction even though the rate of attaining true equilibrium may be very low. At intermediate values of pH, false equilibrium curves (*i.e.*, curves based on measurements in which the time of shaking, though constant, is not adequate for the attainment of true equilibrium at all acidities) will follow a course such as *GH"I*, the greatest errors occurring in the region where the extraction approaches 100%. False equilibrium curves may thus form a sort of hysteresis loop *GH"IH'G* enveloping the true equilibrium curve *GHI*.

The Rôle of the Solvent and Kinetic Aspects of Partition Equilibria.—In considering the effect of changing the solvent on the extraction of a particular metal by a given reagent, two effects must be distinguished. The first concerns the new position of extraction equilibrium; the second involves the kinetics of the equilibration process.

Consider the partition of a metal as governed by equations (9) and (8). Changing the solvent will not alter K_c or K_r but will involve new values p_c' and p_r' for the partition coefficients of the complex and reagent respectively in the new solvent. If [H] and [H]′ are the hydrogen-ion concentrations at which the same extractability E is attained in either case with the same excess reagent, it can easily be shown that

$$[H]/[H]' = (p_r/p_r')^n/(p_c/p_c') \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (14)$$

Data on the effect of a change of solvent on the value of partition coefficients are meagre and the theoretical treatment is too involved to be of value here. At best one can infer from measurements on the solubilities of non-polar substances in a range of organic solvents (cf. Hildebrand, " Solubility," New York, 1936, p. 165) and from relevant partition data that if, for one substance, r, $p_r/p_r' = a > 1$ on change of solvent, the partition coefficient of another non-polar material, c, not too unlike the first, will be changed in the same sense and to much the same extent, *i.e.*, $p_c/p_c' = b > 1$, and $a \sim b$. At least for multivalent metals ($n > 1$), the probable effect of a change to a solvent in which the reagent and its metal complexes are more soluble will be to shift the extraction curves towards regions of higher pH. It is well known that metal " dithizonates " are more soluble in chloroform than in carbon tetrachloride; the same is true of the reagent dithizone itself (see following paper), and in the case of every metal–dithizone extraction curve we have examined that in chloroform lies in a more alkaline region than that in carbon tetrachloride. An additional effect, of some analytical importance, is that extraction curves for a given pair of elements are better separated in the former solvent; but the data need extending to other solvents and other metal–reagent systems.

The rate at which a metal complex appears in the organic phase during the process of extraction depends upon the rates of two separate processes, *viz.*, the formation of metal complex (which may reasonably be expected to take place in the aqueous phase) followed by its (partial) transfer into the organic phase. Partition equilibria of such reagents as oxine and dithizone between water and organic solvents are established very rapidly—certainly within a minute's shaking (cf. following paper) and under optimum conditions extraction equilibrium between metal ions and an organic solution of a reagent is attained equally rapidly, which proves that the partition of the inner-complex is not significantly slower The rate-determining stage in the attainment of extraction equilibrium is thus that of forming the metal complex in the aqueous phase. Since this is strongly influenced (retarded) by hydrogen ions, it can scarcely be due wholly to reactions between metal ions and undissociated reagent. If the rate is a simple function of the activities of the reacting species we can write

$$\text{rate } (r) = k\{M^{n+}\}\{R^-\}^n = k\{M^{n+}\}(p_r K_r f_R - [HR]_o/\{H\}_w)^n \quad . \quad . \quad . \quad . \quad (15)$$

from equations (3) and (5). The rate of attaining equilibrium should thus depend upon the product $p_r K_r$, which is a characteristic of the reagent–water–solvent system. It will be proved in the following paper that $-\log_{10} p_r K_r = pH_{\frac{1}{2}}$, the hydrogen-ion exponent at which the reagent is equally partitioned between water and the organic phase.

If r' is the rate of reaction when another solvent is used, the pH and ionic strength of the aqueous buffer, and the concentration of metal and excess reagent, remaining the same,

$$r/r' = (p_r K_r/p_r' K_r')^n \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (16)$$

For dithizone the values of $p_r K_r$ are $1{\cdot}26 \times 10^{-9}$ and $2{\cdot}75 \times 10^{-11}$ in carbon tetrachloride and chloroform respectively, whence we deduce that the rate of attaining equilibrium in a metal–dithizone system should be about 46^n times slower in the latter solvent. Preliminary experiments gave a factor of 30 in the case of zinc extraction which suggests that the rate-determining stage may involve only one dithizonate ion. Theory predicts that the rate factor due to a change of solvent should be independent of pH and the nature of the metal involved. Experimental confirmation will be reported elsewhere.

Competitive Complex Formation.—Putting $n = 1$ in equation (13) gives the equation to the curve which describes extraction in any univalent metal–reagent–solvent system, its position along the pH axis being determined by the appropriate values of $pH_{\frac{1}{2}}$ and $[HR]_o$. Regarding the hydrogen ion merely as a particular example of a univalent kation, the same equation describes how the percentage of hydrogen bound as complex (*i.e.*, as the undissociated acid HR) and extracted into the organic phase will increase as the pH rises. At first sight this would appear to contradict experience, for as the aqueous phase becomes more alkaline, more and more reagent acid passes into it as the anion R^-. The paradox arises from the unequal rates of diminution of the terms $[HR]_o$ and $[H^+]$ as shown in Table II for the reagent dithizone at a total concentration of 10^{-5}M. Here $p_c \equiv p_r$ and $K_c \equiv K_r$, so the extractability constant, K, of equation (8) is unity; similarly, from equation (11), $pH_{\frac{1}{2}} = -\log_{10}[HR]_o$.

TABLE II.

pH.	4.	5.	6.	7.	8.	9.	10.	11.
$p = [R^-]_w/[HR]_o$ *	$0{\cdot}0_63$	$0{\cdot}0_53$	$0{\cdot}0_43$	$0{\cdot}0_23$	0·003	0·03	0·275	2·75
$[R^-]_w \times 10^7$	$0{\cdot}0_43$	$0{\cdot}0_33$	$0{\cdot}0_23$	0·03	0·27	2·68	21·6	73·3
$[HR]_o \times 10^7$	~100	~100	~100	99·97	97·73	97·32	78·4	36·7
$[H^+]_w$	10^{-4}	10^{-5}	10^{-6}	10^{-7}	10^{-8}	10^{-9}	10^{-10}	10^{-11}
Percentage of hydrogen bound as the complex $[HR]_o$.....	9·1	50	90·9	99·0	99·9	99·99	≈100	

* Partition coefficients calculated for the partition of dithizone between chloroform and water assuming that p_0 is negligible (cf. following paper)

Although this unconventional aspect of the partition of an acidic reagent is of less practical use than that developed in the following paper, it serves to emphasise the universal validity of equations (9) and (13) and the fact that no essential distinction need be drawn between the partition equilibrium of an acidic reagent and its metal complexes. Indeed, if the effect of an acid in decomposing a metal complex may be regarded as a competition between hydrogen ions and metal ions for the anions of the reagent (equation 1), Fig. 1 may equally be taken as representing the simultaneous partition of two complexes in equilibrium with each other through the common anion R^- in the aqueous phase. No new equations are thus required when considering the extraction of admixtures of complexes KR_j, LR_k, MR_l . . . of the same reagent, and little

extra complication is introduced when two reagents HR and HS compete for a common kation (and hydrogen ions).

Now, in deriving the foregoing equations it was postulated that the total concentration of metal in each system could be expressed as the sum of three terms $[M^{n+}]_w$, $[MR_n]_o$, and $[MR_n]_w$, of which the third could generally be neglected. But should the metal ion form a complex soluble in water but insoluble in an organic solvent an extra term must be introduced into the denominator of (6). If the hydrophilic complex is of sufficient stability, the concentration of free metal ions will be so reduced that even under the most favourable conditions of extraction the amount held in the organic phase may be negligible. Good use is made of this effect in reversion procedures (Irving, Andrew, and Risdon, *Nature*, 1948, **161**, 805; this vol., p. 537) and when it is desired to extract one substituent in the presence of others which can be retained selectively in the aqueous phase as stabler complexes. The decreased extraction often noted in the case of amphoteric metals when the pH of extraction exceeds the optimum for 100% extraction is due to the removal of metal ions as complex anions of comparable or greater stability.

When determining traces of metals by extractive techniques, the concentration of salts in the buffer mixtures used to adjust the pH of the aqueous phase to its optimum value is relatively so large that conditions especially favourable to competitive complex formation are set up. Citrates, tartrates, and cyanides in the buffers are particularly effective, but the high concentration ratio of buffer to trace-metal ions may give significance even to relatively unstable complexes with ions such as acetate and borate which are often present. Even when the metal–reagent complex is of great stability, the tendency of the buffer constituents to form competitive hydrophilic complexes is often reflected in the displacement of the extraction curve towards regions of higher pH. Changes in the composition of the aqueous phase may thus alter the amount of metal extracted at equilibrium even when the pH and amount of excess reagent are kept the same (cf. Biefeld and Patrick, *Ind. Eng. Chem. Anal.*, 1942, **14**, 275, for a discussion of lead–dithizone curves). Large changes in ionic strength and specific salt effects will also influence the rate of attaining equilibrium [cf. equation (15)].

In view of the many factors which complicate the study of metal–reagent–water–organic solvent systems in true partition equilibrium, it is scarcely surprising that the data found in the literature, though self-consistent and reproducible under carefully defined conditions and of great value in elaborating arbitrary analytical procedures, must nevertheless be considered of insufficient accuracy for testing the conclusions arrived at above. The omissions will be rectified in subsequent papers.

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395. *Studies with Dithizone. Part II. Dithizone as a Monobasic Acid.*

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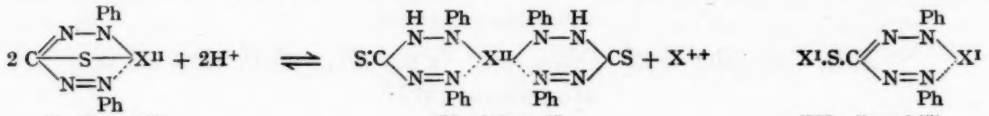
The assumption implicit in all previous work that metal complexes of dithizone result from the replacement of one (or more) of its hydrogen atoms is proved true for the silver complex. Attempts to determine the basicity of dithizone by conventional methods failed owing to its virtual insolubility in water. However, dithizone and the yellow " dithizonate " ion obey Beer's law, and spectrophotometric measurements in a water–alcohol–chloroform monophase showed that its acid strength was intermediate between that of methyl-red and bromothymol-blue with $pK = 5{\cdot}25 \pm 0{\cdot}15$. The partition coefficients of dithizone between aqueous buffers and carbon tetrachloride, chlorobenzene, and chloroform severally were measured over the range pH 4—13. Combined with measurements of p_0, the partition coefficient of undissociated dithizone, they demonstrate that it is a monobasic acid with pK $5{\cdot}77 \pm 0{\cdot}25$: no indication of a second stage of ionisation was obtained. An explicit relationship of general applicability is deduced between the percentage of material extracted and the pH of the aqueous phase in terms of $pH_{\frac{1}{2}}$, the pH at which the partition coefficient is unity (50% extraction). This magnitude (which is simply related to p_0 and pK) is shown to be a characteristic of extraction curves all of which have the same form and are completely superimposable by lateral displacement. Molecular-weight determinations by ebullioscopic and isopiestic methods confirm the absence of association in a dilute solution of dithizone. Attention is drawn to the possibilities of internal hydrogen bonding in dithizone, its anion, and metal complexes.

ALTHOUGH " dithizone " (diphenylthiocarbazone) (IV) is undoubtedly one of the most valuable and widely used organic reagents for the colorimetric determination of trace metals, few of its

metal complexes have been obtained in a state of purity or completely analysed and nothing is known of their structure. Of the structural formulæ proposed by Fischer (*Angew. Chem.*, 1934, **47**, 685; 1937, **50**, 919) and extensively quoted (cf. Sandell, " Colorimetric Determination of Trace Metals," New York, 1944, pp. 74, 397), it may be said that some are stereochemically impossible (*e.g.*, I) and others are improbable (II; cf. Pfeiffer and Glaser, *J. pr. Chem.*, 1938, **151**, 134), whilst confirmatory evidence is lacking in all cases. It should be emphasised that spectrophotometric studies of dilute solutions of dithizone and its metal complexes cannot do more than demonstrate how many molecules of dithizone reagent have interacted with one equivalent of metal. Thus the formula PbDz for lead " dithizonate " (Liebhavsky and Winslow, *J. Amer. Chem. Soc.*, 1937, **59**, 1966), later revised to $PbDz_2$ (Clifford, *J. Assoc. Offic. Agric. Chem.*, 1943, **26**, 26), or the formulæ AgDz, $HgDz_2$ . . . . $BiDz_3$ (Irving, Andrew, and Risdon, this vol., p. 539) assume implicitly that dithizone is behaving as a monobasic acid in forming these complexes.*

Owing to the low percentage of hydrogen in the metal dithizonates, the difficulty of obtaining them as pure solids, and the fact that they may contain water (*e.g.*, $ZnDz_2,H_2O$; Fischer, *Annalen*, 1882, **212**, 316; $ZnDz_2,\frac{1}{2}H_2O$, Irving and Williams, unpublished observation), it is difficult to obtain formal proof that one (or more) hydrogen atom is replaced by a metal in complex formation and the possibility of the reagent being simply co-ordinatively attached (cf. thioacetamide in its argentous complex, $[Ag \leftarrow (S{:}CMe{\cdot}NH_2)_4]$; Cox, Wardlaw, and Webster, *J.*, 1936, 776). That dithizone itself displays acidic character follows from the fact that, though very insoluble in water, it dissolves readily in aqueous alkali to give a yellow solution from which it is re-precipitated on acidification. The decrease in pH when a neutral solution of a silver salt is shaken with dithizone (p. 1853) is a direct proof that metal atoms displace hydrogen in the formation of the complex. The influence of pH upon the extractability of metals by dithizone (cf. Sandell, *op. cit.*) confirms this, and the successful quantitative treatment of the zinc–dithizone system (Kolthoff and Sandell, *J. Amer. Chem. Soc.*, 1941, **63**, 1906; Irving and Williams, unpublished) depends *inter alia* on the assumption that the reagent behaves as a monobasic acid.

Now Fischer postulates that all metal dithizonates can exist in so-called keto-forms in which the hydrogen atom of one phenylimino-group is replaced by metal (as II). Such complexes form preferentially in acid or neutral solution, but in basic solutions or with a deficiency of dithizone they pass over into " enol " complexes (as I or III) derived from the thiol form of the reagent by the loss of two hydrogen atoms. The evidence for such changes of composition (erroneously referred to as tautomerism) is qualitative and scanty and would appear to be based largely upon observations of the copper–dithizone system (Fischer and Leopoldi, *Wiss. Veröff. Siemens-Konzern*, 1933, **12**, 44) though neither the violet-red " keto " nor the yellow-brown



(I; " enol.") (II; " keto.") (III; " enol.")

(X^I and X^{II} are univalent and bivalent metals, respectively.)

" enol " complex has been obtained pure and characterised. The implication that dithizone has *two* dissociable hydrogen atoms is, however, inevitable and in connection with an extended study of metal–dithizone systems we decided to examine the behaviour of dithizone as an acid and to evaluate at least its first dissociation constant, which is of importance when considering the extent of partition of the reagent between aqueous buffers and an immiscible organic phase (p. 1850; cf. Irving, Andrew, and Risdon, this vol., p. 541) and the extent to which the extraction of a metal–dithizone complex is influenced by pH (Irving and Williams, preceding paper).

Krebs and Speakman (*J.*, 1945, 593) have shown that the dissociation constant of a sparingly soluble acid can be calculated from its solubility, S, in various buffer solutions and the solubility, S_0, of the undissociated acid. The method failed with dithizone for in the time required to reach saturation considerable decomposition had taken place in the more alkaline solutions, whilst in neutral or acid solutions the solubility was too small to be measured accurately.

* Most authors (cf. Sandell, *op. cit.*) write Dz as the symbol for dithizone itself and Dz′ for the *uncharged* residue $C_{13}H_{11}N_4S$. We suggest that this confusing and ambiguous nomenclature should be abandoned in favour of HDz for the acidic reagent dithizone ($C_{13}H_{12}N_4S$), reserving Dz for the uncharged residue $C_{13}H_{11}N_4S$, and Dz′ for the singly charged dithizonate anion.

Graphical extrapolation did not give a reliable value for S_0, and although it proved possible to measure $(S - S_0) \propto [Dz']$ absorptiometrically, a direct determination of S_0 failed owing to the virtual insolubility of the reagent in dilute acids or neutral solutions. For the same reason conventional physical methods (pH titration, conductivity measurements, etc.) were equally inapplicable.

Preliminary measurements having shown that the ionisation of dithizone was complete at about pH 10·5, and that the yellow solution of its ions ($\lambda_{max.} = 405$ mμ) obeyed Beer's law up to $E(0{\cdot}25 \text{ cm.}) = 0{\cdot}5$, we proposed to measure the optical density in a series of buffers of decreasing pH and thus to obtain a measure of the variation in [Dz'] whence the dissociation constant could be calculated (cf. Michaelis and Gyemant, *Biochem. Z.*, 1920, **109**, 165; 1921, **119**, 307). But when even the smallest quantity of an alcoholic solution of dithizone which was sufficient to give a measurable optical density when dissolved in dilute ammonia (complete ionisation) was added to a buffer of pH 7 or 8·5, the resulting yellow solution had a definite pink hue and gave a positive Tyndall cone test showing that part of the dithizone had been thrown out of solution as a colloid.

When ammonia gas is passed into a chloroform solution of dithizone a deep red solid separates which must be an unstable ammonium salt since it readily loses ammonia and regenerates dithizone. Similarly the addition of *n*-butylamine to a solution of dithizone in chlorobenzene changed the colour from green to red, the change being more or less reversed by adding varying amounts of acetic acid (or phenol), the exact hue depending upon the relative amounts of green reagent and red dithizonate ion. Attempts to follow the equilibrium spectrophotometrically and hence to determine the relative acidities of dithizone and acetic acid (or phenol) in chlorobenzene, and thence the dissociation constant of the former in water (Griffiths, *J.*, 1938, 818), were fruitless since the optical density of the mixed solutions varied with time and in such a way as to preclude any simple and reliable extrapolation to equilibrium conditions.

It is well known that solutions of dithizone in chloroform give two absorption bands with $\lambda_{max.}$ 605 and 445 mμ (in carbon tetrachloride, 615 and 446 mμ), the first being the more intense. Though insoluble in water and but sparingly soluble in alcohol, dithizone dissolves well in a monophase consisting of 20% water, 30% chloroform, and 50% ethyl alcohol, and when acid is added there results a green solution with $\lambda_{max.}$ 595 and 440 characteristic of the (presumably) undissociated molecule. When alkali is added the colour changes to red and the absorption spectrum now shows a single absorption band with $\lambda_{max.}$ 485 corresponding with that of the dithizonate ion already observed in aqueous solution ($\lambda_{max.}$ 465 mμ) or in chlorobenzene ($\lambda_{max.}$ 490). By additions of drops of an appropriate buffer a series of solutions were prepared containing the same total concentration of dithizone but varying proportions of the undissociated acid and its ion. The transmittancy of these solutions was measured at 485 and 598 mμ, and the pH at which the dithizone was 50% dissociated was found to be 6·3 and 6·4, respectively. The pH of the lightly buffered solutions was measured with a glass electrode–standard calomel cell combination, and it need scarcely be pointed out that neither they nor the average value of 6·35 for the pK of dithizone in the mixed solvent can be directly correlated with similar measurements in aqueous solution. However, evidence from another direction (p. 1850) suggested that the dissociation constant of dithizone in water was of the order of 10^{-4}, whilst the indicators bromothymol-blue and methyl-red are known to be somewhat weaker and stronger acids with pK values of $7{\cdot}1 \pm 0{\cdot}05$ and $5{\cdot}10 \pm 0{\cdot}05$, respectively. Using the same mixed solvent and procedures as in the case of dithizone, spectrophotometric measurements gave the values $8{\cdot}45 \pm 0{\cdot}05$ and $6{\cdot}2 \pm 0{\cdot}1$ for their acid exponents in this medium. There is no reason to suppose that the order of acid strengths in the mixed solvent, *viz.*, methyl-red > dithizone > bromothymol-blue, will not be preserved in water. Since the mixed solvent is markedly protophilic, containing as it does 70% of aqueous alcohol, we may further assume that the relative strengths of these acids will not be seriously affected by change of solvent, whence by linear interpolation of pK values we calculate the dissociation constant of dithizone in water to be $5{\cdot}6 \times 10^{-4}$ ($\pm 40\%$) or p$K = 5{\cdot}25 \pm 0{\cdot}15$.

The extent to which aqueous alkaline solutions will extract dithizone is of great importance in trace-metal analysis (Irving, Andrew, and Risdon, *loc. cit.*), but no systematic study has yet been undertaken though several qualitative observations and a few measurements by Clifford and Wichmann with chloroform and carbon tetrachloride have been recorded (*J. Assoc. Offic. Agric. Chem.*, 1936, **19**, 130). Apart from their intrinsic interest such data should be capable of demonstrating whether dithizone can behave as a polybasic acid and, as the following treatment will show, should afford data for the respective dissociation constants. Though we shall specify

dithizone as the solute, the treatment is generally applicable to other acids which fulfil the necessary conditions and, with obvious modifications, to the partition of bases between aqueous buffers and an immiscible organic phase.

If dithizone, HDz, exists in both water and organic solvents as unassociated molecules and ionises only in the former, its partition coefficient, p, will be given by

$$p = \frac{\text{total concentration of dithizone in water}}{\text{total concentration of dithizone in organic layer}}$$

$$= \frac{[HDz]_w + [Dz']_w}{[HDz]_o} \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad (1)$$

where the subscripts w and o refer to the aqueous and the organic phase respectively. When the acidity is sufficiently high to repress the ionisation of the acid completely, the partition coefficient becomes $p_0 = [HDz]_w/[HDz]_o$, the constant value for undissociated dithizone. $K_1 = \{H\}_w[Dz']_w/[HDz]_w$ being written for the Brønsted (first) dissociation constant, equation (1) reduces to

$$p = p_0 + p_0K_1/\{H\}_w \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad (2)$$

A plot of p against $1/\{H\}_w$ should thus be a straight line with slope p_0K_1 and intercept p_0. The corresponding equation for a dibasic acid would be

$$p = p_0 + p_0K_1/\{H\}_w + p_0K_1K_2/\{H\}_w^2 \quad \ldots\ldots\ldots\ldots \quad (3)$$

so that a plot of p against $1/\{H\}$ would be curved, the curvature becoming more pronounced as the pH rises, though the deviation from linearity may be small if K_2 is very small.

Chlorobenzene was found to be an excellent solvent for dithizone, yielding stable green solutions ($\lambda_{max.}$ 618 and 442) in which Beer's law was obeyed up to at least $E(1\text{ cm.}) = 0{\cdot}75$. The concentration of dithizone in this solvent and in chloroform and carbon tetrachloride (cf. Irving, Andrew, and Risdon, *loc. cit.*) could readily be determined absorptiometrically before and after shaking with an equal volume of an aqueous buffer, and in this way the partition coefficient was determined for each of these solvents over the range of pH 4—13. Changes of phase ratio on mixing were eliminated by pre-saturating the aqueous buffers with organic solvent and the dithizone solution with water. Scrupulous care was taken to remove all traces of metal from the solvents, buffer solutions, and apparatus used, and the successful avoidance of metal contamination was demonstrated in several cases by obtaining identical partition coefficients in the presence of, and in the absence of 2 : 3-dimercaptopropanol (BAL) (cf. Irving, Andrew, and Risdon, *loc. cit.*). Plots of p against $1/\{H\}$ (not reproduced) were linear; the long graphical extrapolation, however, could scarcely be expected to give reliable values for the partition coefficients of the undissociated dithizone but at least showed that they were very small. On the other hand, the slopes of the graphs gave excellent values for the characteristic product p_0K_1 (*q.v.*).

So long as p_0 is small compared with p, equation (2) can be expressed in the logarithmic form

$$\log_{10} p = \log_{10} p_0 - pK_1 + pH \quad \ldots\ldots\ldots\ldots \quad (4)$$

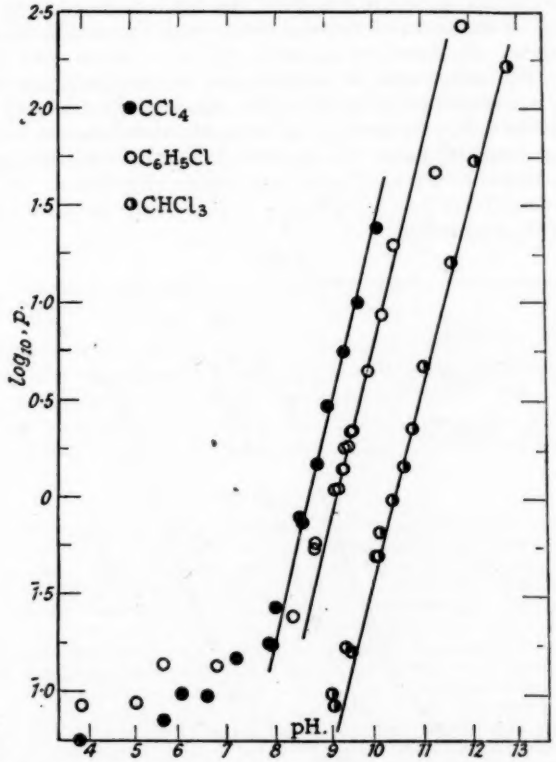
so the graph of $\log_{10}p$ against pH should be a straight line of unit slope. With increasing acidity of the aqueous phase the slope should diminish and the value of the ordinate will approach $\log_{10}p_0$ asymptotically. Were dithizone a dibasic acid, it follows from equation (3) that the $\log_{10}p$–pH plot would be segmented, and the slope would change from 1 to 2 as the influence of the second stage of acid dissociation becomes more pronounced. The graph of the experimental data shown in Fig. 1 shows conclusively that dithizone behaves as a purely monobasic acid, and in confirmation of the absorption spectra obtained in aqueous solutions of various alkalinities it affords no indication of a second stage of ionisation at least over the range pH 4—12. If effective at all in aqueous solution, the second stage of ionisation of dithizone must be that of a very weak acid with $K_2\ 10^{-12}$.

At low pH values the experimental points show a marked scatter (Fig. 1) and extrapolation to obtain values of p_0 is again impracticable. Since, however, the magnitude of the partition coefficient must be independent of phase volumes, a direct determination of p_0 was attempted by partitioning dithizone between the organic solvent and 50 and 75 times its volume of N/100-hydrochloric acid. The values $6{\cdot}4 \pm 1{\cdot}7 \times 10^{-4}$ and $3{\cdot}3 \pm 0{\cdot}3 \times 10^{-4}$ were obtained for carbon tetrachloride and chlorobenzene, respectively. Combining these with the corresponding values of the products p_0K_1 derived from plots of equation (2) or (4), *viz.*, $1{\cdot}26 \times 10^{-9}$ and $3{\cdot}4 \times 10^{-10}$, we arrive at values of 5·61 and $5{\cdot}94 \pm 0{\cdot}15$ for the acid exponent of dithizone. The average value $5{\cdot}77 \pm 0{\cdot}25$ is in satisfactory agreement with that obtained

spectrophotometrically (p. 1849) and we adopt $pK = 5{\cdot}5 \pm 0{\cdot}3$ as a working value. All measurements were made at room temperature (20° ± 5°). The value of p_0K_1 for chloroform was found to be $2{\cdot}75 \times 10^{-11}$, whence p_0 is calculated as $1{\cdot}3 \times 10^{-6}$, a value below the range of direct measurement.

Although equation (2) successfully represents the variation of partition coefficient with hydrogen-ion activity, a simple relationship between the pH of the aqueous phase and the

FIG. 1.



percentage of dithizone extracted into it would be of greater practical value. Writing equation (2) in the logarithmic form

$$\log_{10}(p - p_0)/p_0 = \log_{10}K_1 + \text{pH}$$

and defining $\text{pH}_\frac{1}{2}$ as that hydrogen-ion exponent of the aqueous phase when the partition coefficient is unity (50% extraction) we have

$$\log_{10}(1 - p_0)/p_0 = \log_{10}K_1 + \text{pH}_\frac{1}{2}$$

Subtracting and rearranging

$$\Delta\text{pH} = (\text{pH}_\frac{1}{2} - \text{pH}) = \log_{10}\left(1 + \frac{1-p}{p-p_0}\right)$$

Since ΔpH is a function of $(1 - p)/(p - p_0)$, we should be able to construct its inverse with p as a function of ΔpH. Explicity

$$\frac{p - p_0}{1 - p} = \frac{\coth(2{\cdot}3026\Delta\text{pH}/2) - 1}{2}$$

and since the percentage of extraction $y = 100p/(1 + p)$, we have

$$y = \frac{50\,(\coth 1{\cdot}1513\Delta\text{pH} + 2p_0 - 1)}{(\coth 1{\cdot}1513\Delta\text{pH} + p_0)} \qquad \ldots\ldots\ldots \quad (5)$$

So long as ΔpH is large and positive ($\text{pH} \ll \text{pH}_\frac{1}{2}$), $\coth 1{\cdot}1513\Delta\text{pH} \to 1$, and equation

(5) correctly predicts the limiting percentage extraction as $100p_0/(1 + p_0)$. If, however, $|(\coth 1{\cdot}1513\Delta pH - 1)| \gg p_0$ equation (5) reduces to

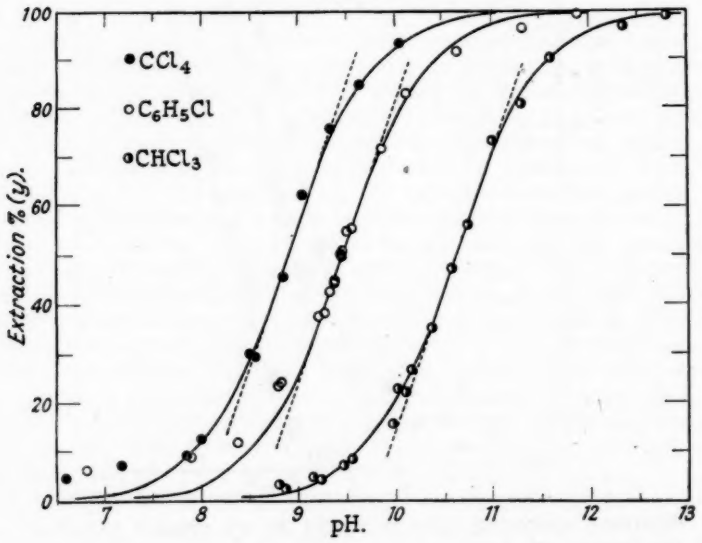
$$y = 50(1 - \tanh 1{\cdot}15\Delta pH) \quad \ldots \quad (6)$$

which reproduces values of y to within 0·1% when $p_0 = 0{\cdot}001$, and within 1% even when p_0 is as large as 0·01. By differentiation

$$dy/d(pH) = 57{\cdot}57(1 - \tanh^2 1{\cdot}1513\Delta pH) \quad \ldots \quad (7)$$

so that the slope at the midpoint where $y = 50\%$ and $\Delta pH = 0$ should be 57·6. Fig. 2 presents the experimental data in the form of plots of percentage extraction against pH. The curves actually drawn are those calculated by equation (6) for systems with pH_i of 8·90, 9·45, and 10·58, respectively. The agreement is remarkably satisfactory especially in the case of chloroform where p_0 is exceptionally small. Too much emphasis need not be laid upon the discrepancies in the more acid solutions in the cases of chlorobenzene and carbon tetrachloride to which both the approximations in the use of equation (6) and the experimental difficulties attaching to measurements of very small partition values contribute. It is not without interest that the simple linear equation $y = 57{\cdot}6[(0{\cdot}87 - pH_i) + pH]$ is quite adequate for any curve over the range 25—75% extraction.

FIG. 2.

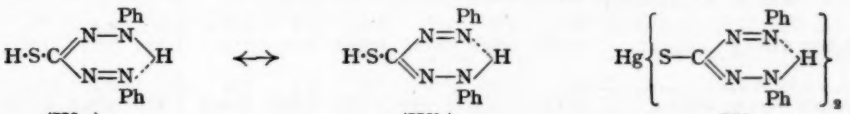


It will be appreciated from equations (6) and (7) and Fig. 2 that *all* extractability curves based on equation (2) are identical in form and can be superimposed by a mere lateral displacement along the abscissa by an amount equal to the difference between their values of pH_i. Since the most accurate measurements of partition coefficients are naturally those for which p equals, or is not far removed from, unity, values of pH_i are more readily determinable than those of the constants p_0 or K_1 to which it is related by the expressions $pH_i = \log_{10}(1 - p_0)/p_0K_1 \cong pK_1 - \log_{10}p_0$. In a subsequent paper we shall discuss the extent to which the characteristic pH_i values for dithizone and the pH values for 50% extraction in a metal–dithizone system preserve the same sequence throughout a series of solvents.

Its high melting point (163°) and sparing solubility in hydrocarbon solvents suggests that dithizone might be associated through S–H–N bonds which are known to be of considerable stability (cf. Hopkins and Hunter, *J.*, 1942, 638). Attempts to determine the molecular weight cryoscopically in benzene, naphthalene and azobenzene proved abortive on account of its low solubility, whilst Rast's method failed owing to the decomposition of dithizone at the melting point of camphor. Indeed, preparative studies (Grummitt and Stickle, *Ind. Eng. Chem. Anal.*, 1942, **14**, 953; Nillman and Cleland, *J. Amer. Chem. Soc.*, 1943, **65**, 1300) generally stress the inadvisability of heating dithizone for long above 50°; but when it was found that the optical density of a solution in chloroform was unchanged after some 10 minutes' heating at 60° an ebullioscopic method seemed practicable. In a Cottrell aparatus the elevation of the boiling

point of a solution containing 1·7 g./l. was but 0·014° (calc. for monomer 0·017°) whilst in a nearly half-saturated solution (4·5 g./l.) the rise was 0·040° (calc. 0·044°). Using Barger's micro-method (*J.*, 1903, **83**, 121), a 0·018M-dithizone solution in chloroform was found to be isopiestic with azobenzene of concentration 0·017 ± 0·002 g.-mol./l. Evidence of association in these strong and obviously non-ideal solutions is thus conflicting. At the most it might amount to 20%, whence we calculate that the association cannot exceed 0·05% in solutions of the concentration (8 mg./l. or less) used in absorptiometric work. This is confirmed by the linear relationship between concentration and optical density found in a wide range of solvents, and by the successful application of equation (2) to problems of dithizone equilibrium, since in its derivation it was postulated that dithizone was unassociated in both water and organic solvent.

Dithizone has been prepared by the reduction of diphenylnitroformazyl with ammonium sulphide (Bamberger, Padova, and Ormerod, *Annalen*, 1926, **446**, 288) and in its thiol form may be formulated as *NN'*-diphenylformazylthiol ("Beilstein," Vol. XVI, p. 26). Like the diarylformazylbenzenes which Hunter and Roberts (*J.*, 1941, 820) showed to be completely



(IV*a*.) (IV*b*.) (V.)

unassociated, it may well be stabilised by internal hydrogen bonding (IV*a* and IV*b*). If further, as seems reasonably certain, ionisation of dithizone involves the hydrogen of the thiol group, the dithizonate anion will be similarly constituted and stabilised. Previous workers have not considered the part which resonance may play in the structure of metal–dithizone complexes. Mercury forms strong bonds with sulphur and its dithizonate could be formulated as (V).

Experimental.

Materials.—All solvents, reagents, buffer solutions, and apparatus were carefully freed from trace metals, and precautions customary in work with dithizone were scrupulously observed (cf. Irving, Andrew, and Risdon, *loc. cit.*). Commercial chlorobenzene was redistilled from an all-Pyrex apparatus, the fraction of b. p. 131—133°/760 mm. being used. When kept in the dark, solutions of dithizone in this reagent showed little loss of strength over a period of some weeks. The solvent is appropriately recovered by the method recommended for chloroform by Biddle (*Ind. Eng. Chem. Anal.*, 1936, **8**, 99). Cotton-wool used in the partition work was freed from metal by repeated extraction with a solution of dithizone in chloroform, washed thoroughly with solvent, and dried in a dust-free atmosphere.

The Formation of the Silver–Dithizone Complex.—20 Ml. of 0·1N-silver nitrate (pH 6·0) were shaken with 10 ml. of dithizone solution (0·5% w./v. in chloroform). The red silver complex formed passed into the organic phase, which was then separated. The extraction was repeated with successive portions of dithizone until the persistence of the green colour showed that removal of silver had been completed. The pH of the aqueous phase was now measured and found to be 1·05, indicating a hydrogen-ion concentration of 0·1N, equivalent to that of the silver ions displaced.

The Yellow Dithizonate Ion.—(a) *Absorption spectra in aqueous solution.* The yellow solutions obtained by adding 5 ml. of a dilute solution of dithizone in alcohol to 35 ml. of 0·15N- or 1·5N-ammonium hydroxide were examined rapidly with a Hilger–Nutting visual spectrophotometer using a 4-cm. cell. The absorption spectra were indistinguishable and showed a single band with $\lambda_{max.}$ 4650 A., the position of which did not change with dilution. A series of solutions were prepared by diluting an arbitrary solution of dithizone in a borax–sodium hydroxide buffer of pH 10·5. The readings (1-cm. cell) on a Spekker absorptiometer using the tungsten lamp with an Ilford Spectrum Blue Filter No. 602 were directly proportional to concentration up to a density of 0·9. With stronger solutions in 0·25-cm. cells the calibration curve was linear up to a density reading of 0·5 and even up to 1·1 the curvature was slight and regular.

(b) *Decomposition in aqueous alkaline solution.* Successive measurement on the same solution of dithizone in 1·5N-ammonium hydroxide at 4650 A. showed that the absorbing species was decomposing at the rate of 20—30%/hour. This rate was not much affected by increased illumination or total exclusion of light, by exclusion of air, or by steady introduction of bubbles of oxygen. Hydroxylamine and traces of metals caused an increase in the rate of decomposition, but sulphite ions appeared to have no influence. The fact that the change was very slow in 0·15N-ammonium hydroxide and accelerated with the alkalinity of the aqueous buffer suggests that a hydrolysis or base-catalysed dismutation is responsible for the decomposition of such solutions.

Spectrophotometric Determination of the Dissociation Constant of Dithizone.—A mixture of 20% water, 50% ethyl alcohol, and 30% chloroform was made from freshly prepared specimens of the purified solvents. Stock solutions of dithizone, methyl-red, and bromothymol-blue were prepared by dissolving sufficient of the pure recrystallised materials to give solutions of an appropriate optical density. By adding 0·05 ml. of an appropriate acid buffer the pH of some of the dithizone solution was adjusted to 2·0 and its absorption spectrum measured with a Beckman Model D.U. Spectrophotometer using a 1-cm. cell and a nominal band width of 1 A. Absorption maxima were noted at 5950 and 4360 A. With

a solution of dithizone at pH 9·5 there was a single band with a maximum at 4850 A. Similar measurements with bromothymol-blue at pH 2·4 and 9·2 gave absorption maxima at 6250 and 4250 A., respectively. Methyl-red showed a maximum at 4150 A. at pH 8·8, but in the acid solutions the absorption band in the green was relatively weak and no determination was made of its position. Buffers (approx. M/50) covering the pH range 2—10 at intervals of about 0·5 unit were prepared from suitable mixtures of hydrochloric acid, potassium hydrogen phthalate, ammonium or sodium acetate, and ammonium hydroxide. 0·05 Ml. of one of these buffers was added to 10 ml. of the stock dithizone solution, and after determination of the optical density (1-cm. cell) at 4850 and 5980 A., the pH was measured with a Cambridge pH-meter. Similar measurements with other buffer mixtures and with methyl-red and bromothymol-blue are reported in the following table.

Optical density of indicators in the mixed solvent.

pH	2·0	3·5	4·6	4·8	5·5	6·0	6·2	6·5	7·1	7·5
Dithizone at 4850 A.	0·165	0·175	0·192	0·205	0·220	0·244	0·268	0·284	0·326	0·350
,, 5980 A.	0·680	0·645	0·582	0·532	0·475	0·414	0·360	0·318	0·217	0·149

pH	8·4	9·0	10·0
Dithizone at 4850 A.	0·378	0·385	0·390
,, 5980 A.	0·102	0·059	0·045

pH	3·5	4·0	5·2	5·4	5·9	6·2	6·5	6·8	7·5	8·0
Methyl-red at 4150 A.	0·635	0·640	0·730	0·800	1·04	1·17	1·46	1·72	1·82	1·84

pH	6·0	7·5	7·9	8·2	8·4	8·5	9·0	9·7	10·0
Bromothymol-blue at 4250 A.	0·410	0·400	0·392	0·373	0·362	0·354	0·319	0·305	0·303
,, 6250 A.	0·010	0·031	0·067	0·107	0·161	0·180	0·285	0·305	0·307

The Partition of Dithizone between Aqueous Buffers and Organic Solvents.—(a) *General method.* 20 Ml. of a solution of dithizone in chloroform (or chlorobenzene or carbon tetrachloride as desired), saturated with water and of an optical density of 0·7 or less, were added to 20 ml. of a metal-free aqueous buffer presaturated with the same solvent and contained in a 125-ml. Pyrex separatory funnel. After being shaken for 1 minute or longer (100 shakes or more by hand, *q.v.*), it was allowed to stand for 2 minutes for the phases to separate. A pledget of metal-free cotton-wool was then inserted into the shortened stem of the funnel, and after rejection of the first few ml. a 1-cm. absorptiometer cell was filled with the organic phase and the optical density (E) was measured with a Spekker absorptiometer using the Ilford Orange filter No. 607. A similar measurement was made on a portion of the original dithizone solution (E_o) and the partition coefficient calculated from the quotient $p = (E_o - E)/E$.

All optical-density readings lay well within the range over which it had previously been shown that the concentration–Spekker reading calibration curve was strictly linear. After separation of the organic phase, the pH of the aqueous phase was measured with a Cambridge pH-meter, corrections for sodium-ion concentration being made (Dole, " The Glass Electrode," Wiley, 1941) where necessary in the more strongly alkaline solutions. At least two measurements were made at each pH and the data given below are the mean of at least two, and sometimes as many as six, concordant measurements.

(b) *Rate of attaining equilibrium.* In this system partition equilibrium is reached very quickly as shown by the following absorptiometer readings:

Solvent.	pH of buffer.	Number of shakes. 0.	30.	50.	100.	200.	400.
$CHCl_3$	~10	0·650	—	—	0·533	0·539	0·535
$CHCl_3$	~ 9	0·650	—	—	0·618	0·614	0·616
CCl_4	8·50	0·540	0·386	0·376	0·376	0·378	—
C_6H_5Cl	9·46	0·691	0·356	0·351	0·351	—	0·352

In the case of chlorobenzene the solutions were equilibrated in a thermostat at 20°, but with the other solvents measurements were made at room temperature which seldom deviated from this by more than a few degrees. The buffer solution used were those recommended by Britton (" Hydrogen Ions," Vol. I, Chapman and Hall, 1942), *viz.*, pH 7·6—9·2, 0·05M-borax and 0·1N-hydrochloric acid; 8·5—9·5, 0·1N-acetic acid and 0·1N-ammonium hydroxide; 9·2—10·0, 0·05M-borax and 0·1N-sodium hydroxide; 10·1—11·4, 0·1M-sodium carbonate and 0·1N-hydrochloric acid; 11·0—12·1, 0·15M-disodium hydrogen phosphate and 0·1N-sodium hydroxide. They were all freed from heavy metals and other impurities which might react with dithizone by methods previously described.

(c) *Results of partition measurements.*

Chloroform.

pH	12·8	12·1	11·6	11·3	11·0	10·77	10·58	10·38	10·11	10·07	10·02
p	90·4	31·1	9·19	4·24	2·69	1·29	0·90	0·546	0·374	0·286	0·300
pH	9·97	9·53	9·47	9·18	9·13	8·85	8·80	3·97			
p	0·264	0·093	0·095	0·050	0·053	0·029	0·036	0·001			

Carbon tetrachloride.

pH	10·03	9·66	9·34	9·05	8·84	8·55	8·50	8·00	7·85	7·18	6·59
p	14·6	5·67	3·16	1·66	0·840	0·421	0·433	0·151	0·102	0·084	0·052
pH	6·07	5·67	4·99								
p	0·054	0·037	0·024								

Chlorobenzene.

pH	11·87	11·30	10·41	10·12	9·86	9·53	9·51	9·46	9·42	9·37	9·33
p	156	26·6	10·9	4·89	2·52	1·26	1·23	1·05	1·01	0·805	0·745
pH	9·28	9·20	8·82	8·80	8·36	7·90	6·81	5·69	5·15	3·98	
p	0·632	0·612	0·333	0·307	0·139	0·101	0·075	0·077	0·047	0·044	

The consistency obtained in such measurements is illustrated by the following data for the distribution of dithizone between carbon tetrachloride and a buffer of pH 8·50 :

E_o	0·540	0·538	0·538	0·540	0·538	0·286	0·286
E	0·373	0·373	0·374	0·379	0·380	0·200	0·200
Percentage extraction	30·93	30·67	30·48	29·82	29·37	30·07	30·07
Partition coefficient	0·448	0·442	0·439	0·425	0·416	0·430	0·430

The presence of adventitious traces of metals capable of reacting with dithizone would diminish the concentration of the green reagent in the organic phase and so lead to incorrect high values for the partition coefficients. Their absence was confirmed by the identity of measurements made in the presence and absence of 2 : 3-dimercaptopropanol using the technique previously described (Irving, Andrew, and Risdon, *loc. cit.*). As a further check, distribution measurements were made in the presence of this reagent (BAL) after varying amounts of copper and lead had been added deliberately to the aqueous buffers. They led to substantially the same partition coefficients as shown by the following representative data :

Measured partition coefficient.	Buffer of pH 10·11 containing Cu (μg.).				Buffer of pH 10·13 containing Pb (μg.).		
	0.	4.	8.	20.	0.	4.	8.
Without BAL	0·363	0·636	1·179	2·774	0·381	0·474	0·667
With 400 μg. BAL	0·360	0·353	0·365	0·353	0·382	0·379	0·380

(d) *The partition coefficient of undissociated dithizone.* If E_o, the initial optical density of a solution of dithizone, is reduced to E on shaking with an equal volume of buffer, the partition coefficient, p, is given by $E = E_o/(1 + p)$. When the phase ratio is increased n-fold, the resulting optical density $E_n = E_o/(1 + np)$, whence $p = (E - E_n)/(nE_n - E)$. Values for p_0 can thus be obtained if the pH of measurement is sufficiently low. 10 Ml. of a solution of dithizone in carbon tetrachloride saturated with water were shaken with 10 ml. of N/100-hydrochloric acid which had previously been freed from all metal impurity and saturated with carbon tetrachloride. Five experiments gave the mean value $E = 0{\cdot}492 \pm 0{\cdot}003$. Extraction of 10 ml. of the same dithizone solution with 500 ml. of the hydrochloric acid gave $E_n = 0{\cdot}477 \pm 0{\cdot}003$, whence $p_0 = 6{\cdot}4 \pm 1{\cdot}7 \times 10^{-4}$. With chlorobenzene $E = 0{\cdot}516 \pm 0{\cdot}001$, and with a phase ratio of 75 : 1, E_n was $0{\cdot}504 \pm 0{\cdot}0003$, whence $p_0 = 3{\cdot}1 \pm 0{\cdot}3 \times 10^{-4}$. Even with a phase ratio of 100 : 1 the values of E_n and E were not significantly different when solutions of dithizone in chloroform were studied.

The Molecular Weight of Dithizone.—Isopiestic measurements using Barger's micro-technique (*loc. cit.*) were carried out in chloroform solution. Pyrex capillaries of about 0·05 mm. diameter were used and incubation at 37° served to hasten the distillation process. In introducing drops of the very concentrated solutions of dithizone alternately with pale yellow solutions of azobenzene, the latter became tinged faintly green and served as most sensitive indicators of the absence of metallic impurities : discoloration led to the rejection of one set of experiments only.

Grateful acknowledgment is made to Imperial Chemical Industries Limited for the loan of apparatus, and to Dr. N. G. Healtey for his invaluable assistance in the micro-determinations of molecular weight.

THE INORGANIC CHEMISTRY LABORATORY, OXFORD. [*Received, February 15th*, 1949.]

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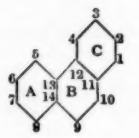
396. *Experiments on the Synthesis of Substances Related to the Sterols. Part XLVIII. Synthesis of a Tricyclic Degradation Product of Cholesterol.*

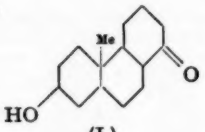
By J. W. CORNFORTH and Sir ROBERT ROBINSON.

A development of the method outlined in Part XLV (*J.*, 1946, 676) has led to the synthesis of the tricyclic diketone (V) in a form structurally and stereochemically identical with a degradation product of cholesterol (Reich, 1945). A summary of this work has already been published (*Nature*, 1947, **160**, 737).

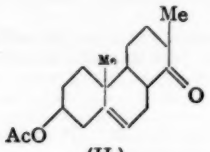
OXIDATIVE degradation of sterols and bile acids has become an important means of preparing hormones and other valuable substances. In such partial syntheses, by-products are sometimes encountered which owe their origin to the removal of ring D of the steroid nucleus. Thus Köster and Logemann (*Ber.*, 1940, **73**, 299) isolated 1-keto-7-acetoxy-2 : 13-dimethyl-$\Delta^{9(14)}$-dodecahydrophenanthrene (II) from the oxidation products of cholesteryl acetate dibromide; hydrolysis and Oppenauer-oxidation of (II) gave the unsaturated ketone (III). Reich (*Helv.*

Chim. Acta, 1945, **28**, 892) similarly obtained 7-hydroxy-1-keto-2 : 13-dimethyl-Δ^{3}-dodecahydrophenanthrene (IV) from methyl diacetyldeoxycholate, and thence by reduction and oxidation 1 : 7-diketo-2 : 13-dimethylperhydrophenanthrene (V).

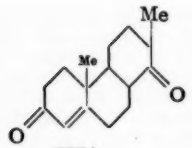




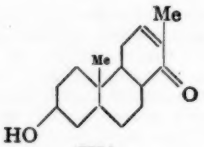
(I.)



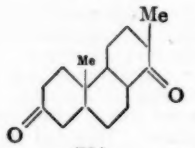
(II.)



(III.)



(IV.)



(V.)

We have now been able to correlate these two series: hydrogenation of (III) led smoothly to (V). Our thanks are due to Dr. K. Miescher and to Prof. T. Reichstein and Dr. H. Reich, who kindly furnished specimens of (II) and (V) respectively.

The method used (Part XLV, *loc. cit.*) to synthesise one stereoisomeride of 7-hydroxy-1-keto-13-methylperhydrophenanthrene (I) from 1 : 6-dihydroxynaphthalene promised an approach to the total synthesis of the steroid nucleus. It was obvious, however, that the completion of the task would be facilitated by a relay at the tricyclic stage. Identification of such a synthetic product with material derived from a natural steroid might have two great advantages. In the first place a large number of possible stereoisomerides would be eliminated from consideration and, secondly, the degradation product, if available in sufficient quantity, might serve as the raw material for the later stages of the synthesis. The diketone (V) was therefore chosen as the first objective: we already had reason to believe that the method used to prepare (I) produced a *cis*-configuration at the A/B ring-junction, and this configuration is present also in (V) because it was prepared from deoxycholic acid without disturbance at $C_{(14)}$ ($C_{(5)}$ in steroid numbering).

It was necessary to repeat the first steps of the synthesis on a much larger scale than heretofore, and we express our gratitude to Messrs. Imperial Chemical Industries Ltd. (Dyestuffs Division), for a generous supply of 1 : 6-dihydroxynaphthalene, prepared specifically for the present investigation. The earlier stages are shown on page 1857.

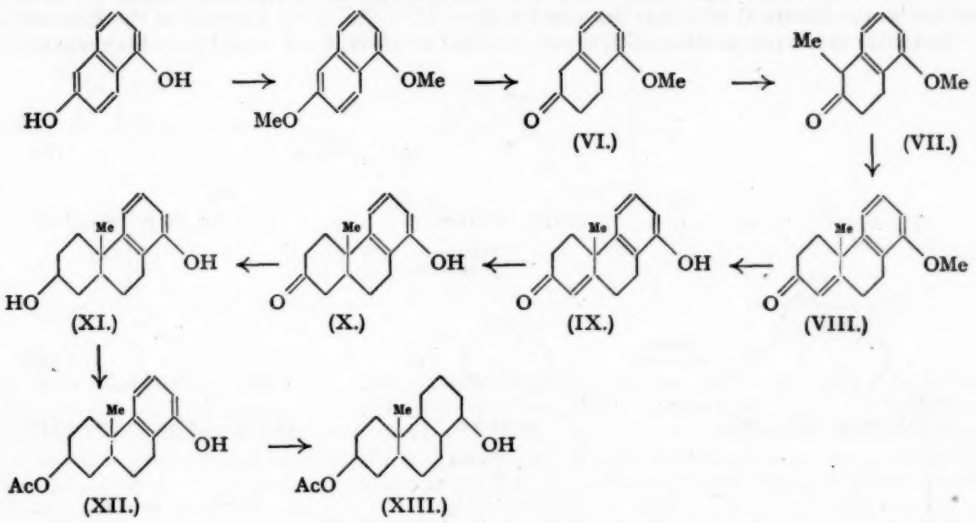
The preparation of 5-methoxy-2-tetralone (VI) in hectogram quantities presented no special difficulty; the *C*-methylation of (VI) was modified to operate in batches of comparable size, and conditions for the separation of 5-methoxy-1-methyl-2-tetralone (VII) from unchanged (VI) and 5-methoxy-1 : 1-dimethyl-2-tetralone were standardised. The latter stage, however, is relatively the least satisfactory of the synthesis (maximum net yield, 62%).

In the next operation a successful departure was made from the usual technique for inducing reaction between alicyclic ketones and diethylaminobutanone methiodide. Instead of preparing a sodio-derivative of the ketone (VII) by means of sodamide and adding an alcoholic solution of the methiodide, the crystalline methiodide was prepared in the reaction vessel, a benzene solution of the ketone added, and reaction initiated by addition of alcoholic potassium ethoxide. The method is well adapted to large-scale working and should be useful when a stronger base than ethoxide ion is required. In the present instance it enabled us to prepare 7-keto-1-methoxy-13-methyl-5 : 6 : 7 : 9 : 10 : 13-hexahydrophenanthrene (VIII) in 70% yield.

Demethylation of (VIII) to 1-hydroxy-7-keto-13-methyl-5 : 6 : 7 : 9 : 10 : 13-hexahydrophenanthrene (IX) by means of hydrogen iodide in acetic acid was repeated with few modifications. Hydrogenation of (IX) was allowed to proceed through 1-hydroxy-7-keto-13-methyl-$\Delta^{1:3:11}$-octahydrophenanthrene (X) to 1 : 7-dihydroxy-13-methyl-$\Delta^{1:3:11}$-octahydrophenanthrene (XI), m. p. 171°. The mother-liquors from which (XI) was separated, doubtless contained the 7-epimeride and this could be oxidized by the Oppenauer method to give a further quantity of (X), and thence, by reduction, (XI).

With methyl sulphate (X) gave the methoxy-ketone that had previously been prepared by hydrogenation of (VIII). Bromination of the methoxy-ketone afforded a bromo-ketone which was evidently 8-bromo-7-keto-1-methoxy-13-methyl-$\Delta^{1:3:11}$-octahydrophenanthrene, because the unsaturated ketone (VIII) was readily regenerated by boiling it with pyridine. This

transformation provided additional evidence that the alicyclic rings in (X) and (XI) were fused in the *cis*-configuration, since it has always been found that the bromination of β-decalones



occurs preferentially at the α-position in *cis*-β-decalones and at the β′-position in *trans*-β-decalones. On the other hand, the suggestion (Part XLV) that the angular methyl and alcoholic hydroxyl groups have a *cis*-relationship in (XI) must now be withdrawn. It has been found that the reduction of (X) to (XI) gives a better yield in alcoholic than in acetic acid solution, so that no analogy with the case of coprostanone can be discerned. Indeed, the results recall the behaviour of 3-keto-groups in the bile acids, which tend to give 3(α)-hydroxy-steroids on reduction under acid or neutral conditions.

The partial acetylation of (XI) to 1-hydroxy-7-acetoxy-13-methyl-$\Delta^{1:3:11}$-octahydrophenanthrene (XII) required no modification. Hydrogenation of the acetoxy-phenol (XII) over platinum in an acetic acid medium was not found satisfactory on a larger scale; the use of Raney nickel in dioxan at high temperature and pressure gave some of the desired product but was attended by too much hydrogenolysis of the 1-hydroxyl group. Palladium–strontium carbonate in dioxan (Morton and Robinson, *J.*, 1943, 497) was the catalyst of choice; at 200° it afforded 1-hydroxy-7-acetoxy-13-methylperhydrophenanthrene (XIII) as a mixture of stereoisomerides in 70% yield.

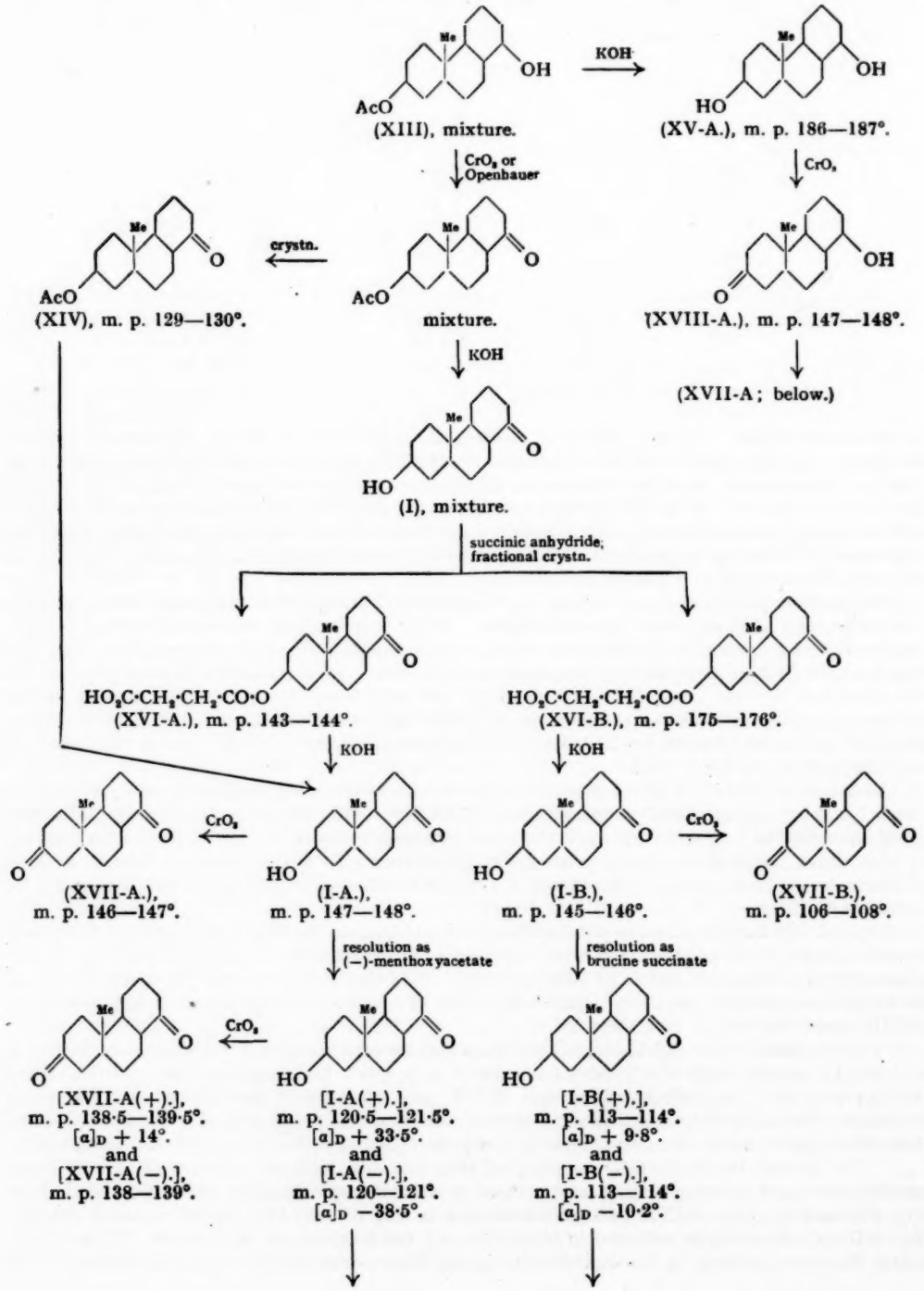
Oxidation of (XIII) with chromic acid or by the Oppenauer method gave a mixture of 1-*keto*-7-*acetoxy*-13-*methylperhydrophenanthrenes* (XIV) from which a crystalline individual could be separated; usually, however, the total oxidation product was hydrolysed. In this way a crystalline, hydrated mixture of hydroxy-ketones (I) was obtained, along with a 1 : 7-dihydroxy-13-methylperhydrophenanthrene (XV), the latter doubtless being derived from unoxidized (XIII).

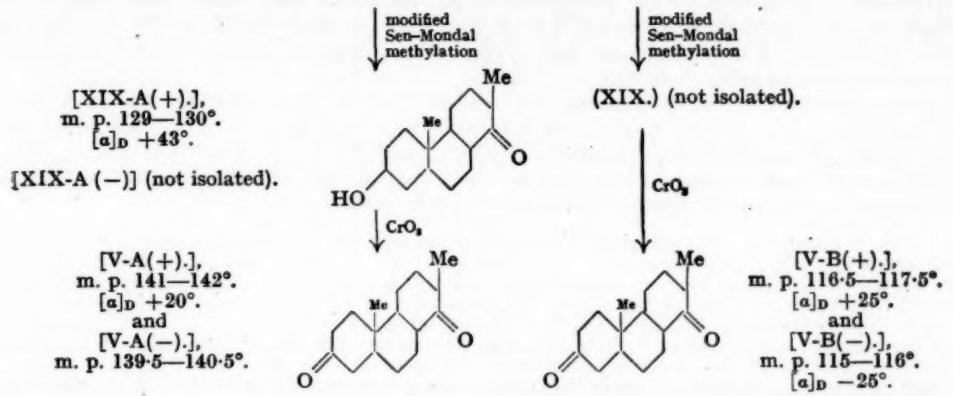
The hydroxy-ketone mixture was treated with succinic anhydride and pyridine; fractional crystallization of the product separated it into two stereoisomeric 1-*keto*-13-*methyl*-7-*perhydrophenanthryl hydrogen succinates* (XVI), and these on hydrolysis gave two 7-*hydroxy*-1-*keto*-13-*methylperhydrophenanthrenes* (I), from which two 1 : 7-*diketo*-13-*methylperhydrophenanthrenes* (XVII) were derived by oxidation.

We have already (Part XLV, *loc. cit.*) given reasons for supposing that the mixture of hydroxy-ketones (I) consists exclusively of *trans*-α-decalone types. Oxidation of the two individual hydroxy-ketones (I) to different diketones (XVII) provides a proof that the stereoisomerism is not wholly due to the 7-hydroxy-group; epimerization of this group is in any event unlikely to have taken place under the conditions of synthesis. Still less likely is a partial inversion at $C_{(14)}$. The probability is thereby established that the two hydroxy-ketones (I) are the two possible racemates, having rings B and C fused in the *trans*-relationship, which can be derived from the acetoxy-phenol (XII) without inversion at any of the existing asymmetric centres. This will not, however, be assumed in what follows; the stereochemical families will be termed A and B, corresponding to the lower-melting and higher-melting hydrogen succinates (XVI)

respectively, the difference between the series being understood to lie in the configuration of the bridgehead carbon atoms $C_{(11)}$, $C_{(12)}$, $C_{(13)}$, $C_{(14)}$.

The A-7-hydroxy-1-keto-13-methylperhydrophenanthrene (I-A) was found to give a semicarbazone identical with that described in Part XLV (*loc. cit.*); presence of the B-isomeride in the earlier crude preparation of (I) is not excluded however, for it would have been masked by

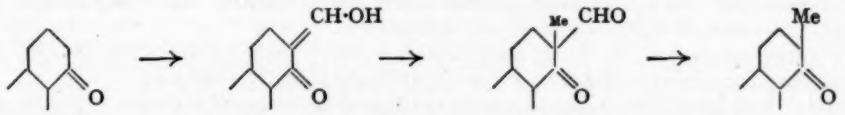




the more abundant A-isomeride. The crystalline acetoxy-ketone (XIV) gave the A-hydroxy-ketone (I-A) on hydrolysis. The diol (XV) mentioned above could be partly oxidized to a hydroxy-ketone differing from both (I-A) and (I-B); further oxidation gave the A-diketone (XVII-A), so that the diol (XV) is of the A series and, if epimerization at $C_{(7)}$ can be excluded, the intermediate oxidation product is *A*-1-*hydroxy*-7-*keto*-13-*methylperhydrophenanthrene* (XVIII).

Optical resolution of (I-A) (the more abundant isomeride) was first undertaken. No satisfactory alkaloidal salt of the hydrogen succinate (XVI-A) having been found, the hydroxy-ketone was esterified with (−)-menthoxyacetyl chloride. The resolution followed a somewhat unusual course: the diastereoisomerides formed a molecular compound of $[\alpha]_D$ about −43°, which was partly dissociated on recrystallisation to give the more sparingly soluble *A*(−)-1-*keto*-13-*methyl*-7-*perhydrophenanthryl* (−)-*menthoxyacetate*. Although several recrystallisations were necessary to separate the maximum amount of this ester, yet, arising from the circumstances mentioned, no progressive changes were observed in the optical rotation of the fractions which consisted of the molecular compound, or of substantially pure A(−)-ester of $[\alpha]_D$ about −77°. The course of resolution could actually be followed without polarimetric control, the form of the crystals being a sufficient guide. Hydrolysis of this A(−)-ester led to *A*(−)-7-*hydroxy*-1-*keto*-13-*methylperhydrophenanthrene* [I-A(−)]. Material in the mother-liquor of the menthoxyacetate crystallisation was similarly hydrolysed and gave a partly racemic product, separated by crystallisation into *A*(+)-7-*hydroxy*-1-*keto*-13-*methylperhydrophenanthrene* [I-A(+)] and a little of the racemic hydroxy-ketone (I-A). Oxidation of the purified enantiomorphs led to *A*(+)- and *A*(−)-1 : 7-*diketo*-13-*methylperhydrophenanthrenes* (XVII).

Introduction of a methyl group at $C_{(2)}$ was now necessary. We had long considered the method of Sen and Mondal (*J. Indian Chem. Soc.*, 1928, **5**, 609) as eminently suitable in a case of this kind. The operations involved are formylation, *C*-methylation, and hydrolysis, as follows:



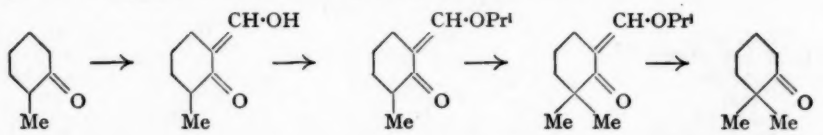
Sometimes the last two stages are combined in one operation.

Accordingly, the hydroxy-ketone [I-A(−)] was formylated, and the sodio-derivative of the resulting crude hydroxymethylene-ketone heated in methanol with methyl iodide. Oxidation of the neutral product gave a new ketone, A(−)-1 : 7-diketo-2 : 13-dimethylperhydrophenanthrene [V-A(−)]. This showed a considerably higher melting-point than the "natural" diketone (V), and thus provided the first indication that the A series was not the desired one.

Resolution of (I-B) was therefore necessary. The hydrogen succinate of (XVI-B) formed diastereosiomeric brucine salts of widely differing solubility, so as to render feasible the separation of brucine B(−)-1-keto-13-methyl-7-perhydrophenanthryl succinate in spite of the very small amount of available material. Successive treatment with acid and alkali gave *B*(−)-1-*keto*-13-*methyl*-7-*perhydrophenanthryl hydrogen succinate* [XVI-B(−)] and then *B*(−)-7-*hydroxy*-1-*keto*-13-*methylperhydrophenanthrene* [I-B(−)]. From the mother-liquors of the

recrystallisation of the brucine salt a crude hydrogen succinate was obtained and most of the sparingly soluble (±)-compound which it contained could be separated from this. After this process, hydrolysis of the remainder and crystallisation yielded *B*(+)-7-*hydroxy*-1-*keto*-13-*methylperhydrophenanthrene* [I-B(+)].

Experience with the Sen–Mondal methylation of [I-A(−)] had indicated the need of a gentler procedure, for, though the desired substance was eventually obtained, the yield and quality of the product were unsatisfactory. Johnson and Posvic (*J. Amer. Chem. Soc.*, 1947, **69**, 1361) have recently published a method for the *C*-methylation of ketones, illustrated below by the stages in the preparation of 2 : 2-dimethyl*cyclo*hexanone.



It will be appreciated that an alkoxymethylene group is here used to block *C*-methylation on one side of the carbonyl group, whereas in the Sen–Mondal method the hydroxymethylene group facilitates *C*-methylation on the same side. *iso*Propyl iodide and potassium carbonate in acetone were used by Johnson and Posvic for *O*-alkylation of the hydroxymethylene-ketone; methyl iodide had been tried first, but had afforded little *O*-methyl ether. It was assumed that *C*-methylation accounted for the rest of the product, and as this seemed probably correct an extremely mild method of carrying out the Sen–Mondal *C*-methylation was indicated.

The hydroxymethylene-ketone obtained by formylation of [I-A(+)] was therefore heated with potassium carbonate and methyl iodide in acetone solution and suspension. Gentle acid hydrolysis followed by extraction with alkali then removed the small proportion of hydroxymethylene-ketone which had undergone *O*-alkylation; the neutral product containing A(+)-7-hydroxy-1-keto-2-formyl-2 : 13-dimethylperhydrophenanthrene was then warmed with alkali. Crystalline *A*(+)-7-*hydroxy*-1-*keto*-2 : 13-*dimethylperhydrophenanthrene* (XIX) could be isolated at this stage, but chromic acid oxidation of the crude product gave the diketone *A*(+)-1 : 7-*diketo*-2 : 13-*dimethylperhydrophenanthrene* [V-A(+)] in better overall yield.

Methylation of [I-B(−)] was now carried out in the same manner. The resulting *B*(−)-1 : 7-*diketo*-2 : 13-*methylperhydrophenanthrene* [V-B(−)] was difficult to purify. This was possibly due to unnecessarily vigorous acid hydrolysis, which may have brought about contamination with some unmethylated diketone in the final product. However, the diketone [V-B(−)] melted at almost the same temperature as the " natural " diketone, and the optical rotation was of the same magnitude though opposite in sign.

Advantage of the experience gained was taken in effecting the *C*-methylation of [I-B(+)]; gentler conditions were used and the product, B(+)-1 : 7-diketo-2 : 13-dimethylperhydrophenanthrene [V-B(+)], was purified without trouble. It had the same melting point and, within experimental error, the same optical rotation as the " natural " diketone (V), and mixed-melting-point determination also indicated the identity of the synthetic and the " natural " specimens. Final confirmation of this, and also of the identity of the two " natural " specimens prepared from cholesterol and from deoxycholic acid, was sought in a comparison of the substances by *X*-ray crystallography. We are indebted for this comparison to Dr. D. M. Crowfoot, F.R.S., whose report follows.

" The three specimens, *A* from cholesterol, *B* from deoxycholic acid (Reich), and *C*, synthetic, were compared and found to be crystallographically identical.

" *A* and *C* had been crystallised in the form of good lath-shaped crystals or prisms suitable for single *X*-ray crystallographic examination. In *B*, the crystals were very small; a portion was therefore recrystallised from a few drops of ether; thin, clear plates formed by evaporation in a few hours.

" The specimens may be described as orthorhombic plates or prisms showing the forms 001, 101, and 011, and usually elongated along 010. The unit cell dimensions are approximately: $a = 8{\cdot}1$, $b = 7{\cdot}22$, $c = 23{\cdot}7$ A.; space group P2,2,2; $n = 4$ for ρ calc. = 1·18. The orientation of the optic axes is $n_\gamma // b$, $n_\alpha // c$, $n_\beta // a$. (19.9.47)."

Experimental.

All optical rotations were taken in chloroform solution. Melting points are uncorrected, a point to be noted because many corrected m. p.s are cited in the literature.

Hydrogenation of 1 : 7-*Diketo*-2 : 13-*dimethyl*-Δ^8-*dodecahydrophenanthrene* (III).—A solution of

1-keto-7-acetoxy-2 : 13-dimethyl-$\Delta^{9(14)}$-dodecahydrophenanthrene (II; 950 mg.) in methanol (15 c.c.) along with potassium hydroxide (1 g.) was heated under reflux for an hour. The neutral product was isolated by means of ether and dissolved in toluene (30 c.c.); water was then expelled by boiling. *cyclo*Hexanone (4 c.c.) and aluminium *iso*propoxide (0·5 g.) were added and the procedure of Köster and Logemann (*loc. cit.*) was then followed. Recrystallisation of the crude product from ether gave a first crop of (III) (443 mg.), m. p. 137·5—138·5°, raised by crystallisation from methanol to 138—139°; $[\alpha]_D$ +124° ± 3° (*c*, 0·716). Köster and Logemann gave m. p. 140—141°, $[\alpha]_D$ 128°. The unsaturated ketone (III) (441 mg.) in ethanol (5 c.c.) was hydrogenated at 20°/1 atm. in the presence of platinum oxide (22 mg.). Hydrogen (50 c.c.) was taken up within 5 minutes, the rate of absorption then slackened, and the process was stopped. Recrystallisation of the product from ether afforded colourless, prismatic rods, m. p. 116·5—117·5°, of 1 : 7-diketo-2 : 13-dimethylperhydrophenanthrene (V; "natural" *A* of Dr. Crowfoot's report); $[\alpha]_D^{24}$ +28° ± 2° (*c*, 1) (Found: C, 77·1; H, 9·5. Calc. for $C_{16}H_{24}O_2$: C, 77·4; H, 9·7%). A specimen of (V) prepared by Dr. H. Reich from deoxycholic acid and very kindly supplied to us, also had m. p. 116·5—117·5° under our conditions (Reich, *loc. cit.*, gáve 119—120·5° as the corrected m. p. on the Kofler block); there was no depression in m. p. on admixture of the specimens.

5-Methoxy-2-tetralone (VI).—1 : 6-Dihydroxynaphthalene (200 g.) was mixed with 2N-sodium hydroxide (1120 c.c.), and methyl sulphate (250 c.c.) added at once. The mixture was shaken and prevented from actually boiling until reaction had subsided; 2N-sodium hydroxide (560 c.c.) and methyl sulphate (120 c.c.) were then added. When the second reaction slackened, excess of methyl sulphate was destroyed by warming for ½ hour on a steam-bath with frequent shaking. The warm liquid was acidified and extracted with chloroform; the chloroformic layer was washed twice with a little 2N-sodium hydroxide and evaporated. Sodium (190 g.) was added during 35 minutes to a solution of the crude 1 : 6-dimethoxynaphthalene (225 g.; 96%) in boiling alcohol (1900 c.c.); a large copper reflux condenser was used. Alcohol (400 c.c.) was then added and heating continued under reflux until the metal had disappeared (about 40 minutes). Water (600 c.c.) was cautiously added and most of the alcohol removed under diminished pressure. The residue was mixed with more water (300 c.c.), and the lower aqueous layer was separated as far as possible and extracted twice with a little dioxan which was then united with the oily upper layer. To this was added water (250 c.c.) and then hydrochloric acid (*d* 1·18) until the mixture was acid to Congo-red (about 100 c.c. required). More acid (30 c.c.) was added and the liquid kept hot and shaken occasionally for ½ hour. The lower oily layer was separated; the aqueous layer was diluted with water (1 l.), separated from more oil, and extracted thrice with small quantities of chloroform. The combined oil and chloroformic extracts were stirred with saturated aqueous sodium hydrogen sulphite (500 c.c.) until crystallisation set in. Next day the mass was triturated with ether; the solid was collected, washed well with ether, dissolved in hot water (2—3 l.) and treated with solid sodium carbonate until no more oil separated. The 5-methoxy-2-tetralone was extracted with chloroform and distilled; b. p. *ca.* 120°/0·5 mm. (157 g.). The material which did not react with sodium hydrogen sulphite could be reduced again with sodium and alcohol, but this gave only an additional 2 g. of ketone (total yield, 73% based on 1 : 6-dihydroxynaphthalene). On keeping, the ketone solidified in massive prisms, m. p. 36—37°.

5-Methoxy-1-methyl-2-tetralone (VII).—An ice-cooled mixture of 5-methoxy-2-tetralone (51 g.), dry methanol (50 c.c.), and methyl iodide (25 c.c.) was stirred under nitrogen during the addition (1 hour) of a solution of sodium (6·6 g.) in dry methanol (100 c.c.). The mixture was stirred for a further hour and then heated under reflux for a few minutes; dilute sulphuric acid was added with good stirring until a colour change (to brighter yellow) indicated that excess of alkali had been destroyed. Air was then admitted, a little water added, and the methanol removed under reduced pressure. The oil was separated and a little more recovered from the aqueous layer by extraction with chloroform. The solvent-free oil was shaken with saturated, aqueous sodium hydrogen sulphite (35 c.c.) until the mixture became solid (5—10 minutes); after 25 minutes had elapsed from the time of mixing, ether was added, to inhibit further reaction, and the solid collected and washed with ether. The bisulphite compound was decomposed as in the previous experiment and gave unchanged (VI) (13·7 g.). The ethereal filtrate was evaporated, the residue mixed with an equal volume of ethanol, shaken with saturated sodium hydrogen sulphite (100 c.c.) until crystallisation set in (about ½ hour), and kept for 36 hours. The bisulphite compound was then collected, washed, and decomposed as before. The crude monomethyl ketone (VII) was tested for unchanged (VI) by dissolving one drop in alcohol (1 c.c.) and adding one drop of 10% sodium hydroxide. A slight purple colour usually appeared at once; if this did not deepen appreciably on shaking for 1—2 minutes, the sample was satisfactory, otherwise treatment with a little more sodium hydrogen sulphite was necessary. The ketone was then distilled; b. p. about 120°/0·5 mm. (21 g.); it sometimes solidified and then had m. p. 42—43° after washing with a little light petroleum, but the entire distillate was used in the next stage. The unchanged (VI) was remethylated without distillation and afforded a further quantity of (VII). From 156 g. of (VI), 85 g. of (VII) and 8·5 g. of recovered (VI) were obtained by two successive methylations, a net yield of 62%.

7-Keto-1-methoxy-13-methyl-5 : 6 : 7 : 9 : 10 : 13-hexahydrophenanthrene (VIII).—Diethylaminobutanone (prepared according to Wilds and Shurk, *J. Amer. Chem. Soc.*, 1943, **65**, 471) (15·05 g.) was swirled gently in a 1-l. flask and cooled in ice during the addition of methyl iodide (15·0 g.) in portions during ½ hour. The swirling was regulated so as to obtain the crystalline methiodide as an even coating on the walls of the flask. When no more liquid remained, the flask was kept in ice for ½ hour and then under the tap for 45 minutes. A solution of the ketone (VII) (20·0 g.) in dry, thiophen-free benzene (100 c.c.) was added, air was expelled from the flask by dry nitrogen, and a solution of potassium (6·5 g.) in dry ethanol (100 c.c.) added with ice cooling during 5 minutes. Swirling was continued until the methiodide had all dissolved (about 30 minutes) and was replaced by a precipitate of potassium iodide. After it had been kept in ice for another hour, the mixture was boiled gently for 25 minutes. An excess of 2N-sulphuric acid was then added and the nitrogen stream stopped. After addition of enough water to dissolve the potassium sulphate the benzene layer was separated and the aqueous layer extracted twice with ether. The united extracts were washed with water, clarified with a little magnesium sulphate, and evaporated. The residue was distilled and 23·2 g. were collected up to 180°/0·1 mm. The distillate was

warmed until fluid, and ether added gradually until the total weight was 40 g. Crystallisation set in at once and was allowed to proceed at 0° overnight; the ketone (VIII) (17·0 g.; m. p. 115—117°) was then collected and washed with chilled ether. The mother-liquors after fractional distillation afforded an additional 1 g.; the total yield was thus 71%. This process has been carried out successfully on four times the above scale.

1-*Hydroxy*-17-*keto*-5 : 6 : 7 : 9 : 10 : 13-*hexahydrophenanthrene* (IX).—Hydriodic acid (51 c.c.; *d* 1·7; light yellow in colour) was added to a boiling solution of the methoxy-ketone (VIII) (68 g.) in pure acetic acid (1020 c.c.). Heating under reflux was continued for 30—35 minutes, and the mixture cooled quickly and poured into a stirred mixture of water (4 l.), containing a little sodium hydrogen sulphite, and ether (400 c.c.). The light-yellow ethereal layer was separated and the aqueous layer shaken twice with ether. The combined extracts were then repeatedly washed with water and finally with small successive portions of 2N-sodium hydroxide until all the acetic acid had been removed. 2N-Sodium hydroxide (140 c.c.) was then added and, after brief shaking, the deep-red lower layer was run into an excess of 2N-sulphuric acid with swirling. The ethereal layer was washed twice with a little water, extracted again with 2N-alkali, and washed again with water and finally with a little 2N-acid. All the alkaline washings were acidified immediately after separation. The precipitated phenol (IX) was collected, washed, dried at 100°, and triturated with cold ether; it was then ready for hydrogenation. From the neutral fraction, unchanged material was recovered by distillation at low pressure; the distillate was then demethylated as before. In this way 37 g. (70% net) of the phenol (IX) were obtained, along with 12 g. of recovered methoxy-ketone.

1 : 7-*Dihydroxy*-13-*methyl*-$\Delta^{1:3:11}$-*octahydrophenanthrene* (XI).—The phenol (IX) (37 g.) and platinum oxide (2·6 g.) were suspended in alcohol (200 c.c.) and hydrogenated at 20°/1 atm. The first stage was very rapid; (IX) dissolved and the saturated ketone (X) separated. Further reduction was slower; it could be accelerated by addition of a trace of ferrous sulphate (50 mg. in a little water). When absorption had ceased, catalyst and solvent were removed, the residue treated with enough chloroform to make it fluid and crystallisation allowed to proceed at 0°. Next day the diol (XI) (24·5 g.) was collected; m. p. 170°. The mother-liquors were reoxidized by the Oppenauer method with acetone (300 c.c.), aluminium *tert.*-butoxide (15 g.), and benzene (300 c.c.) (heating for 24 hours under reflux), and the product was isolated in the usual way and stirred for several hours with saturated aqueous sodium hydrogen sulphite solution, but no crystalline adduct separated. The mixture was washed with ether, and the aqueous layer and gummy precipitate were treated with an excess of sodium carbonate solution and extracted with ether. Crystallisation from ethanol gave the phenolic ketone (X), from which more of the diol (XI) (3·5 g.) was obtained by hydrogenation. The total yield of (XI) and (IX) combined was therefore 75%.

Transformation of the Phenolic Ketone (X) *into the Unsaturated Methoxy-ketone* (VIII).—1-Hydroxy-7-keto-$\Delta^{1:3:11}$-octahydrophenanthrene (0·7 g.) was methylated with methyl sulphate and N-sodium hydroxide in the usual manner to give 7-keto-1-methoxy-$\Delta^{1:3:11}$-octahydrophenanthrene (0·6 g.), m. p. 119—121° after crystallisation from ether. The m. p. was not depressed by admixture with material previously prepared (Part XLV, *loc. cit.*) by hydrogenation of (VIII). This methoxy-ketone (548 mg.) in acetic acid (7 c.c.) was treated with bromine (360 mg.) in acetic acid (1·8 c.c.). The deep-blue solution was diluted with water, and the product collected and crystallised from a little alcohol. Another recrystallisation gave 8-*bromo*-7-*keto*-1-*methoxy*-$\Delta^{1:3:11}$-*octahydrophenanthrene* as aggregated, colourless prisms, m. p. 136—137° (Found: C, 59·3; H, 5·9; Br, 23·8. $C_{16}H_{19}O_2Br$ requires C, 59·5; H, 5·9; Br, 24·8%). The bromo-ketone (400 mg.) was boiled with dry pyridine (12 c.c.) for 20 hours. Ether and dilute acid were added; the ethereal solution was dried, treated with charcoal, and evaporated. The residual gum crystallised on seeding with (VIII). Two crystallisations from light petroleum (b. p. 40—60°) gave colourless, prismatic needles, m. p. 118—120°, alone or mixed with a specimen of (VIII), m. p. 119—120°.

1-*Hydroxy*-7-*acetoxy*-13-*methyl*-$\Delta^{1:3:11}$-*octahydrophenanthrene* (XII).—The partial acetylation of (XI) (27·95 g.) was carried out as before (*loc. cit.*) affording (XII) (20·3 g.; recrystallised). After hydrolysis of the acetate in the mother-liquor, 9·8 g. of (XI) were recovered (net yield, 95%).

Hydrogenation of (XII).—The acetoxy-phenol (XII) (12·8 g.) in dioxan (190 c.c.; peroxide-free and anhydrous) was hydrogenated for 3 hours at 190—205°/*ca.* 150 atm. in the presence of palladium–strontium carbonate (6·5 g. of 2·5%), only a trace of the phenol escaping reaction. Distillation gave a lower fraction, b. p. 90—100°/0·005 mm., consisting largely of hydrogenolysed material (4·0 g.); the main fraction (8·3 g.) containing 1-hydroxy-7-acetoxy-13-methylperhydrophenanthrenes (XIII) distilled at 130—140°/0·01 mm. and was a vitreous mass when cold. A small further quantity could be recovered on redistillation of the lower fractions. In an earlier experiment when the hydrogenation was interrupted prematurely, the unchanged acetoxy-phenol (XII) crystallised out almost quantitatively when the product was (without distillation) mixed with an equal volume of ether and kept for a few days.

Oxidation of (XIII).—(*a*) The above glassy product (17·9 g.; b. p. 130—140°/0·1 mm.) in purified acetic acid (180 c.c.) was treated slowly at 10—20° with chromium trioxide (4·8 g.) in a little water and acetic acid (180 c.c.). After 22 hours the mixture was diluted with water (1500 c.c.) and extracted twice with ether. The clear yellow extract, freed from acetic acid, was evaporated, and the residue partly crystallised. This was dissolved in alcoholic potassium hydroxide (400 c.c of 0·4N), and the solution heated under reflux for one hour, concentrated to 150 c.c., and slowly diluted to 1 l. with water.

The crystalline precipitate (9·75 g.) was collected and recrystallised from moist ethyl acetate, giving a fraction (7·2 g.) melting indefinitely below 100°, consisting of hydrated hydroxy-ketones (I). The mother-liquor and aqueous-alcoholic filtrate were united and extracted continuously with ether; the product was treated with aqueous-alcoholic semicarbazide acetate and gave a crystalline semicarbazone mixture (4·1 g.). This was decomposed by keeping with a 15% solution of oxalic acid in methanol; the product on crystallisation from moist ethyl acetate gave a further 2·2 g. of the hydroxy-ketone mixture. From the semicarbazone mother-liquors a crystalline product, m. p. 181—182°, was obtained (0·8 g.); recrystallisation from ethyl acetate gave fine needles, m. p. 186—187°, of *A*-1 : 7-*dihydroxy*-13-*methylperhydrophenanthrene* (XV) (Found: C, 75·1; H, 10·6. $C_{15}H_{26}O_2$ requires C, 75·6; H, 10·9%).

(*b*) The glassy fraction, b. p. 130—140°/0·01 mm. (0·6 g.), was boiled under reflux for 45 hours with acetone (20 c.c.), benzene (20 c.c.), and aluminium *tert.*-butoxide (1 g.). The isolated product was crystallised from a little alcohol, giving 1-*keto*-7-*acetoxy*-13-*methylperhydrophenanthrene* (XIV) (150 mg.) in fine, solvated needles, m. p. 129—130°, after drying for several hours at 30°/15 mm. (Found: C, 73·4; H, 9·4. $C_{17}H_{26}O_3$ requires C, 73·5; H, 9·4%). After hydrolysis of the substances in the mother-liquors, the diol (XV) was obtained.

1-*Hydroxy*-7-*keto*-13-*methylperhydrophenanthrene* (XVIII).—A mixture of the diol (XV) (780 mg.), chromium trioxide (290 mg.), and acetic acid (15 c.c.) was kept for 24 hours. The neutral product was crystallised thrice from ethyl acetate, giving the *hydroxy-ketone* (XVIII) (0·3 g.) as colourless prisms, m. p. 147—148°, depressed sharply by both hydroxy-ketones-I-A and -I-B (Found: C, 76·4; H, 10·0. $C_{15}H_{24}O_3$ requires C, 76·2; H, 10·2%). The substances reacted with dinitrophenylhydrazine and with succinic anhydride in pyridine. On admixture with the diketone (XVII-A) there was a small but definite lowering of the m. p. (to 143—144°). The substance (110 mg.) was oxidised further with chromium trioxide (75 mg.) in acetic acid (3 c.c.). After 20 hours the product was isolated as usual and crystallised from ethyl acetate; m. p. 146·5—147·5°, alone or mixed with (XVII-A) (diketone), m. p. 146—147°.

1-*Keto*-13-*methyl*-7-*perhydrophenanthryl Hydrogen Succinates* (XVI-A) *and* (XVI-B).—The hydrated mixture of hydroxy-ketones (I) (8·2 g.) was heated with succinic anhydride (8 g.) and pyridine (16 c.c.) at 120° until a sample gave a clear solution in aqueous sodium carbonate (about 2 hours). An ether–chloroform solution of the product was washed with dilute acid and then repeatedly with water, evaporated to a syrup, and treated with ether (25 c.c.). Large prisms (6·9 g.), m. p. 140—141·5°, gradually separated; as soon as the crystallisation appeared complete the liquid was decanted and the crystals were washed quickly with ether. The mother-liquors and washings were evaporated to a syrup, using a little methanol to inhibit immediate crystallisation, then treated with ether, and allowed to crystallised as completely as possible. This gave a mixed crop (2·5 g.) which was dissolved in methanol, evaporated to a syrup, and treated with ether (10 c.c.). Irregular nodules (0·4 g.), m. p. 172—174°, separated; the mother-liquor was decanted before any of the prismatic form had separated, and evaporated with methanol. Ether (6 c.c.) was added and the volume maintained constant during the crystallisation. The crystals were separated by hand, giving 1·05 g. of prisms, m. p. 132—140°, and 1·0 g. of nodules, m. p. 155—165°. The prisms were recrystallised from ethyl acetate, and the purified product (0·65 g.) was united with the prisms obtained previously; recrystallisation of a sample from ethyl acetate gave the *A-hydrogen succinate* (XVI-A) as colourless prisms, m. p. 143—144° (Found: C, 67·6; H, 8·7; equiv., 335. $C_{19}H_{28}O_5$ requires C, 67·8; H, 8·4%; equiv., 336). Recrystallisation of the combined crops of nodules (m. p. 172—174° and 155—165°) from ethyl acetate (charcoal) gave the more sparingly soluble *B-hydrogen succinate* (XVI-B) in colourless, aggregated leaflets (1·05 g.), m. p. 175—176° (Found: C, 68·1; H, 8·4%). By similar processes the mother liquors gave small additional amounts of (XVI-A) and (XVI-B).

7-*Hydroxy*-1-*keto*-13-*methylperhydrophenanthrenes* (I-A) *and* (I-B).—The A-hydrogen succinate (200 mg.) was hydrolysed by warming with potassium hydroxide (0·3 g.) in water (8 c.c.) on a steam-bath for 20 minutes. After the mixture had cooled, the crystals were collected and recrystallised from moist ethyl acetate; m. p. about 100°. By drying for 2½ hours at 80°/15 mm. the anhydrous *hydroxy-ketone* (I-A) was obtained, having m. p. 147—148°; it formed prisms on recrystallisation from light petroleum (b. p. 60—80°) (Found: C, 76·1; H, 10·0. $C_{15}H_{24}O_2$ requires C, 76·3; H, 10·2%). The semicarbazone separated from *iso*butanol in diamond-shaped prisms, m. p. 245° (decomp.) undepressed by admixture with the semicarbazone described in Part XLV (*loc. cit.*). The same hydroxy-ketone, m. p. and mixed m. p. 147—148°, was obtained by hydrolysis of the acetoxy-ketone (XIV).

The B-hydrogen succinate (200 mg.) was hydrolysed in the same manner. The product on recrystallisation from ethyl acetate gave the anhydrous *hydroxy-ketone* (I-B) in colourless rectangular rods, m. p. 145—146°, depressed sharply by (I-A) (Found: C, 76·7; H, 10·1. $C_{15}H_{24}O_2$ requires C, 76·3; H, 10·2%). The *semicarbazone* crystallised from butanol in aggregated leaflets, m. p. 226—227° (decomp.) (Found: N, 13·7. $C_{16}H_{27}O_3N_3$ requires N, 14·3%).

1 : 7-*Diketo*-2 : 13-*dimethylperhydrophenanthrenes* (XVII-A) *and* (XVII-B).—A solution of hydroxy-ketone (I-A) (75 mg.) and chromium trioxide (30 mg.) in acetic acid (2 c.c.) was kept for 12 hours. The *diketone* (XVII-A) separated from ethyl acetate in well-formed, thick plates, m. p. 146—147°, depressed sharply by admixture with the parent hydroxy-ketone (Found: C, 76·8; H, 9·5. $C_{15}H_{22}O_2$ requires C, 76·9; H, 9·5%). The *bis*-2 : 4-*dinitrophenylhydrazone* was prepared by adding the diketone (16 mg.) to a solution of 2 : 4-dinitrophenylhydrazine (50 mg.) and a little sulphuric acid in alcohol (10 c.c.) and digestion of the mixture at the boiling point until the precipitate became granular; recrystallisation from dioxan gave small, orange-yellow prisms, m. p. 256—257° (decomp.) (Found: C, 54·7; H, 5·3. $C_{27}H_{30}O_8N_8$ requires C, 54·5; H, 5·1%).

Hydroxy-ketone (I-B) (72 mg.) was oxidized as described for (I-A); the *diketone* (XVII-B) was recrystallised by adding light petroleum to a solution in a little chloroform, and filtering quickly; it formed colourless leaflets, m. p. 106—108° (Found: C, 76·6; H, 9·4%). The *bis*-2 : 4-*dinitrophenylhydrazone* was prepared as in the A series; it separated from dioxan–alcohol in isolated, orange-yellow prisms, m. p. 257—258° (decomp.) depressed to 245—246° by admixture with the A-derivative (Found: C, 54·9; H, 5·2; N, 18·3. $C_{27}H_{30}O_8N_8$ requires C, 54·5; H, 5·1; N, 18·8%). It is uncertain whether the bisdinitrophenylhydrazone reported in Part XLV (*loc. cit.*) was of the A or B series, for all of the older sample was consumed for analysis; most likely it was of the more abundant A series.

Resolution of the Hydroxy-ketone (I-A).—The hydrogen succinate (XVI-A) (7·01 g.) was hydrolysed as described above, and the resulting hydroxy-ketone (I-A) freed from water by heating at 100°/15 mm. The hydroxy-ketone (4·90 g.) in anhydrous pyridine (25 c.c.) was treated with (−)-menthoxyacetyl chloride (5·3 g.; distilled) dropwise with swirling. After 24 hours the mixture was poured into water (400 c.c.), set aside with a little ether for 2 hours, and then extracted with ether, which was washed with 3N-hydrochloric acid, N-sodium hydroxide, and water, filtered through a little magnesium sulphate, and evaporated, finally *in vacuo*. The residue was mixed with an equal volume of light petroleum (b. p.

40—60°), cooled to about −40°, removed from the cooling bath, and scratched. The mass soon became solid; it was taken up in boiling light petroleum (15—20 c.c.) and set aside at 0°. Next day the crystals (7·0 g.; fluffy needles) were collected; m. p. 75—78°; $[\alpha]_D^{21}$ −43° (*c*, 1). A second crop (0·65 g.) was obtained by concentration of the mother-liquor to a small volume; this had m. p. 75—77° and $[\alpha]_D^{20}$ −45° (*c*, 1).

The subsequent course of the resolution can be recorded most succinctly by describing the recrystallisation of a typical fraction. This fraction (3·45 g.), m. p. 77—80°, $[\alpha]_D^{20}$ −45°, was boiled with light petroleum (b. p. 40—60°; 20 c.c.), leaving a slight residue of larger prisms. On cooling a further crop of prisms separated; this was collected after 1 hour and had m. p. 105—108°, $[\alpha]_D^{21}$ −76° (*c*, 1). The mother-liquor was concentrated to about 10 c.c. and kept at 0° overnight; a crop of fluffy needles (0·68 g.) was then collected; m. p. 77—79°; $[\alpha]_D^{24}$ −43° (*c*, 1). This crop was united with others of similar m. p. and specific rotation, and recrystallised as above to give more prisms.

The combined crops of prisms, m. p. 105° to 110°, $[\alpha]_D$ −75° to −77°, were recrystallised twice from ethyl acetate to give *A*(−)-1-*keto*-13-*methyl*-7-*perhydrophenanthryl menthoxyacetate*, m. p. 112—113°; $[\alpha]_D^{23}$ −77° ± 2° (*c*, 1) (Found: C, 74·6; H, 9·9. $C_{27}H_{44}O_4$ requires C, 75·0; H, 10·2%). The total amount obtained was 3·0 g. This product (2·85 g.) was heated under reflux with potassium hydroxide (1 g.) in methanol (12 c.c.) for 2½ hours; water was added and the mixture extracted thrice with chloroform. Some of the product was crystallised from ethyl acetate and some from chloroform–light petroleum (b. p. 40—60°); in each case long, colourless needles of *A*(−)-7-*hydroxy*-1-*keto*-13-*methylperhydrophenanthrene* [I-A(−)] were obtained; m. p. 120—121°; $[\alpha]_D^{23}$ −33·5° ± 2° (*c*, 1); this was a hydrate, and the m. p. was not changed by heating for several hours at 100°/20 mm. or by subliming at 120°/0·1 mm. (Found: C, 71·1; H, 10·5. $C_{15}H_{24}O_3,H_2O$ requires C, 70·9; H, 10·2%). The yield was 1·55 g.

The mother-liquors of the (−)-menthoxyacetate crystallisation, from which as much as possible of the material of $[\alpha]_D$ −43° had been separated, gave a gum on evaporation. This was hydrolysed with potassium hydroxide in methanol as described for the A(−)-ester. The crude product was recrystallised, first from ethyl acetate–light petroleum and then from large volumes of light petroleum (b. p. 40—60°); the light-petroleum solutions were concentrated to half their bulk before crystallisation was allowed to take place. In this way mixed crops of slender colourless needles and larger, slightly yellow prisms were obtained; the prisms were picked out where possible, and advantage was also taken of their slower rate of dissolution in light petroleum. The first crystallisation gave mixed material of m. p. 116—117·5° and $[\alpha]_D^{23}$ +31·5°; the prisms were gradually eliminated and finally a total of 1·35 g. of *A*(+)-7-*hydroxy*-1-*keto*-13-*methylperhydrophenanthrene* [I-A(+)] was obtained having m. p. 120—121·5°, and $[\alpha]_D^{24}$ +38·5° ± 2° (Found: C, 70·8; H, 10·3 $C_{15}H_{24}O_3,H_2O$ requires C, 70·9; H, 10·2%). As with the A(−)-siomeride, the water of crystallisation could be demonstrated by boiling the substance with benzene. The prisms separated by recrystallisation (0·25 g.) had m. p. 144—145°, undepressed by anhydrous (±)-A-hydroxy-ketone (I).

A(−)- *and A*(+)-1 : 7-*Diketo*-13-*methylperhydrophenanthrenes* (XVII).—The hydroxy-ketone [I-A(−)] was oxidized with chromic acid in the manner already described. The *diketone* [XVII-A(−)] separated from ether in clusters of prisms, m. p. 138—139° (Found: C, 77·0; H, 9·5. $C_{15}H_{22}O_2$ requires C, 76·9; H, 9·5%).

From the hydroxy-ketone [I-A(+)] the *diketone* [XVII-A(+)] was prepared similarly; small prisms from ether; m. p. 138·5—139·5°; $[\alpha]_D^{26}$ +14·5° ± 2° (*c*, 0·4) (Found: C, 76·7; H, 9·2%).

A(−)-1 : 7-*Diketo*-2 : 13-*dimethylperhydrophenanthrene* [V-A(−)].—The hydroxy-ketone [I-A(−)] (200 mg.) was boiled with benzene until free from water. The solution was mixed with ethyl formate (0·3 c.c.) and added to powdered potassium (50 mg.) in benzene (3 c.c.). Next day, water and ether were added; the aqueous layer was washed with ether, and the benzene–ether layer was extracted with N-sodium hydroxide, which was then added to the aqueous layer. Acidification and ether extraction gave the crude hydroxymethylene ketone (140 mg.; dried at 100°/20 mm.). This was heated with methyl iodide (0·3 c.c.) and a solution of sodium (11·5 mg.) in methanol (0·5 c.c.) under pressure at 100° for 6 hours. The product was boiled with N-hydrochloric acid for a few minutes and then taken up in ether, and a little hydroxymethylene ketone extracted with alkali; the neutral fraction obtained on evaporation of the ethereal solution was then extracted with light petroleum (b. p. 40—60°). The resulting yellow, petroleum-soluble gum was set aside in acetic acid (2 c.c.) with chromium trioxide (50 mg.). Next day the mixture was worked up as usual and the crystalline, neutral product recrystallised from ether–light petroleum (b. p. 40—60°) and then from ethyl acetate–light petroleum. The *diketone* [V-A(−)] formed small prisms, m. p. 139·5—140·5° (Found: C, 77·3; H, 9·6. $C_{16}H_{24}O_2$ requires C, 77·4; H, 9·7%). On admixture with the diketone [XVII-A(−)] the m. p. was depressed to 110°.

Resolution of the Hydroxy-ketone (I-B).—The hydrogen succinate (XVI-B) (11·319 g.) and anhydrous brucine (13·231 g.) were dissolved in acetone, and the solution was concentrated to 10 c.c. and set aside for 48 hours at 0°. The stout prisms (1·45 g.) were then collected; m. p. 129—130° (effervescence); $[\alpha]_D^{20}$ −41° (*c*, 1). Two recrystallisations by dissolution in chloroform, concentration to a syrup, and addition of acetone (8 c.c.) gave a product (1·20 g.), m. p. 132·5—133·5° (effervescence) and $[\alpha]_D^{20}$ −43°, unchanged by further crystallisation. A solution of this product in chloroform–acetone was poured into a mixture of hydrochloric acid (0·6 c.c.; *d* 1·18) and water (9 c.c.); the organic solvents were then removed by gentle heating at low pressure. The crystalline residue was triturated under several changes of water and then dried by evaporation of added carbon tetrachloride. The residue separated from ether–light petroleum (b. p. 40—60°) in irregular platelets, m. p. 116—117°, $[\alpha]_D^{21}$ −23° ± 2°, of *B*(−)-1-*keto*-13-*methyl*-7-*perhydrophenanthryl hydrogen succinate* [XVI-B(−)] (Found: equiv., 334. $C_{12}H_{28}O_5$ requires equiv., 336). The crystals and mother-liquor were warmed with dilute aqueous potassium hydroxide, and the neutral hydrolysis product crystallised from ether–light petroleum (b. p. 40—60°) (1 : 1). *B*(−)-7-*Hydroxy*-1-*keto*-13-*methylperhydrophenanthrene* [I-B(−)] was thus obtained in fine needles of a hemihydrate (280 mg.), m. p. 113—114°, $[\alpha]_D^{23}$ −10·2° ± 0·5° (*c*, 4·18) (Found: C, 73·5; H, 10·5. $C_{15}H_{24}O_3,0{\cdot}5H_2O$ requires C, 73·4; H, 10·4%). The m. p. was not changed by prolonged heating at 80° *in vacuo*.

The mother-liquor from the initial crystallisation of brucine salt was evaporated and treated as above to recover the hydrogen succinate. This was left overnight in ether (1 c.c.), after nucleation with the (±)-hydrogen succinate (XVI-B). The solution was then decanted from the few crystals of (XVI-B) which had separated; after being washed with dilute hydrochloric acid the ether was removed and the residue warmed with aqueous potassium hydroxide. The neutral product on crystallisation from ether, gave long needles, m. p. 105—106°, apparently of a more solvated form, which reverted on drying at 80°/15 mm. to the hemihydrate (203 mg.), m. p. 113—114°, $[\alpha]_D^{20}$ +9·3° ± 0·5° (*c*, 4·16), of *B*(+)-1-*hydroxy*-7-*keto*-13-*methylperhydrophenanthrene* [I-B(+)] (Found: C, 73·8; H, 10·4. $C_{16}H_{24}O_2,0{\cdot}5H_2O$ requires C, 73·4; H, 10·4%). In order to test the optical purity of this product it was crystallised (*a*) from light petroleum (75% recovery) and (*b*) from benzene (50% recovery). The crystals obtained from (*a*), and both crystals and mother-liquor from (*b*), showed the same specific rotation as the original material.

A(+)-1 : 7-*Diketo*-2 : 13-*dimethylperhydrophenanthrene* [V-A(+)].—A benzene solution of the hydroxy-ketone [I-A(+)] (236 mg.) was boiled to expel water of crystallisation. A benzene suspension of sodium methoxide (from 92 mg. of sodium) was mixed with ethyl formate (0·33 c.c.) and the solution of the hydroxy-ketone; the volume was made up to 25 c.c. with benzene, and the mixture kept over-night in the absence of air. Water was then added; the benzene layer was twice extracted with N-sodium hydroxide, and the united alkaline solutions washed once with ether and acidified with hydrochloric acid. Extraction with ether and evaporation, finally at 80°/0·4 mm., gave the crude hydroxymethylene-ketone as a light-yellow gum (218 mg.). This was dissolved in acetone (1·25 c.c.) and heated under reflux with potassium carbonate (118 mg.; freshly ignited) and methyl iodide (0·2 c.c.) for 20 hours. The product was isolated and kept in 0·5N-aqueous-alcoholic hydrochloric acid for 2 hours; recovered hydroxymethylene-ketone was then removed by extraction with N-sodium hydroxide. The neutral fraction (150 mg.) slowly developed a faint colour with alcoholic ferric chloride; it was accordingly warmed for a few minutes with 2N-aqueous-alcoholic hydrochloric acid and then extracted with alkali as before. Hydrolytic removal of the formyl group was then carried out by gently heating the neutral product with potassium hydroxide in methanol (1 c.c. of 10%) for 10 minutes. After isolation in the usual way the neutral product was oxidised by means of chromium trioxide (50 mg.) in acetic acid (3 c.c.). Next day, the customary procedure gave the *diketone* [V-A(+)], m. p. 136—138° (100 mg.); recrystallisation from ether afforded colourless prisms, m. p. 141—142°, $[\alpha]_D^{25}$ +20° ± 2° (*c*, 1·36) (Found: C, 77·4; H, 9·6. $C_{16}H_{24}O_2$ requires C, 77·4; H, 9·7%). A mixture with the diketone [XVII-A(+)] had m. p. 110°.

The crude product before oxidation could be crystallised from light petroleum (b. p. 40—60°) to give small needles, m. p. 129—130°, $[\alpha]_D^{17}$ +43° ± 2° of *A*(+)-7-*hydroxy*-1-*keto*-2 : 13-*dimethylperhydrophenanthrene* [XIX-A(+)]. This apparently contained a trace of water not expelled by prolonged heating at 100° *in vacuo* (Found: C, 75·5, 75·8; H, 10·3, 10·4. $C_{16}H_{26}O_2$ requires C, 76·8; H, 10·4%). On admixture with the hydroxy-ketone [I-A(+)] (hydrate) the m. p. was intermediate. The presence of the 2-methyl group was confirmed by chromic acid oxidation, the product being the diketone [V-A(+)]. An alternative explanation of the low carbon content found in this case is that the product contained a little of the unchanged formyl derivative ($C_{17}H_{26}O_2$ requires C, 73·4; H, 9·3%). It is important to notice that the chromic acid oxidation would correct any incompleteness of hydrolysis, since $-CHO \longrightarrow -CO_2H \longrightarrow H$ (CO_2).

B(−)- *and* *B*(+)-1 : 7-*Diketo*-2 : 13-*dimethylperhydrophenanthrenes* [V-B(−)] *and* [V-B(+)].—Formylation and methylation of the hydroxy-ketone [I-B(−)] (150 mg.) was carried out as described for [I-A(+)] above. Acid hydrolysis of the total methylation product was carried out by warming for 15 minutes with 3N-aqueous-alcoholic hydrochloric acid. The subsequent operations again followed the procedure given above. The *diketone* [V-B(−)], after one recrystallisation from ether and two from light petroleum, had m. p. 115—116°, $[\alpha]_D^{25}$ −25° ± 2° (Found: C, 77·5; H, 9·8. $C_{16}H_{24}O_2$ requires C, 77·4; H, 9·7%).

The formylation and methylation of [I-B(+)] (175 mg.) were carried out as already indicated; all extractions with alkali, however, were done at 0° to minimise loss of the formyl group by hydrolysis. After the methylation, acid hydrolysis was effected by keeping with 1·5N-aqueous-alcoholic hydrochloric acid; alkaline extraction (at 0°), hydrolysis, and oxidation then followed as in the A(+)-series. The diketone [V-B(+)] (58·5 mg.) had m. p. 115·5—116·5° after one crystallisation from light petroleum (b. p. 40—60°); recrystallisation gave colourless rods or blades, m. p. 116·5—117·5°, $[\alpha]_D^{25}$ +25° ± 2° (*c*, 1·3) (Specimen *C* of Dr. Crowfoot's report) (Found: C, 77·2; H, 9·7. Calc. for $C_{16}H_{24}O_2$: C, 77·4; H, 9·7%). There was no depression in melting point on admixture with the specimen of (V) prepared from cholesterol.

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397. *Experiments on the Synthesis of Substances related to the Sterols. Part XLIX. The A ⟶ BCD Route to Androstenedione. Part II.*

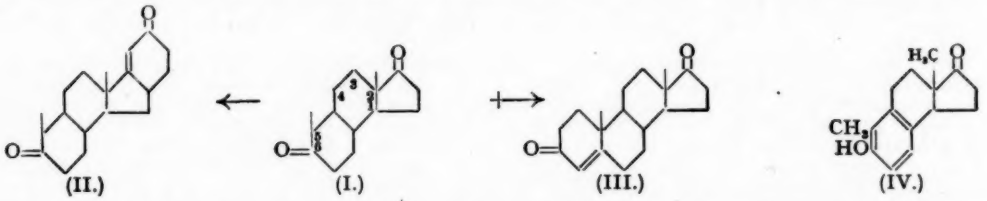
By R. H. Martin and Sir Robert Robinson.

Further examination of the condensation of 4-diethylaminobutan-2-one methiodide and 3′ : 6-diketo-2 : 5-dimethyldecahydro-1 : 2-*cyclo*pentenonaphthalene-x-α (I) in the presence of sodium ethoxide, has shown that the main product at least is a derivative (II) of 1 : 2-benzfluorene and not, as was hoped, of 1 : 2-*cyclo*pentenophenanthrene (cf. III). This follows from a comparison of ultra-violet absorption of substances obtained from the condensation product on the one hand, and a mixture of *cis*- and *trans*-androstenediols on the other, by successive reduction, dehydration, and dehydrogenation.

In order to render the continuation of the synthesis by this route feasible, it will be necessary to prepare a keto-alcohol related to (I) and in which the keto-group is in position 6 of the reduced naphthalene nucleus. Some observations of a miscellaneous character are included, partly bearing on this problem, and partly relating to matters encountered at various stages of the synthesis of (I).

In Part XLI (*J.*, 1943, 491) the present authors described the synthesis of two inactive stereoisomerides of the phenolic ketone (IV), and the diketone (I) was obtained from the more abundant α-isomeride by catalytic reduction followed by oxidation.

An individual compound (I) was isolated but in order to determine the course of the condensation with the Mannich-base methiodide, a mixture of stereoisomerides resulting at the hydrogenation stage was employed. The product was a viscous oil showing the absorption spectrum of an αβ-unsaturated ketone. We had good reason to expect the formation of (III)



from analogy with the behaviour of 1-methyl-2-decalone (Robinson and Weygand, *J.*, 1941, 386). It was clearly stated, however, that we had not been able to establish the constitution of the product; we considered the position that would confront us if the condensation had taken the course to (II) (or another undesired direction not indicated above), and in the experimental section we discussed only the ketones, $C_{19}H_{26}O_2$, without naming them.

In the event we have found the mixture of ketones, $C_{19}H_{26}O_2$, to consist chiefly of substances of the structure (II) though we cannot exclude the formation of a small proportion of stereoisomerides (III) (or of the third type resulting from attack of position 7 of the decalone nucleus).

The only possible method of investigation was clearly by degradation to a recognisable aromatic hydrocarbon and we first practised with androstenedione.

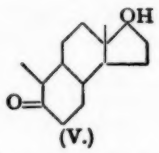
We are very grateful to Messrs. Organon Laboratories and in particular to Dr. C. L. Hewett for gifts of androstenedione and androstenediol.

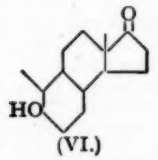
Androstenedione was reduced by means of sodium and *n*-propanol and the resulting diol was dehydrated by heating with potassium hydrogen sulphate. After dehydrogenation with selenium at 320—340°, the product was chromatographically purified and then crystallised. Its ultra-violet absorption spectrum showed that it was a derivative of 1 : 2-*cyclo*pentenophenanthrene and it was probably essentially the 3′-methyl derivative of this hydrocarbon.

The unsaturated ketones, $C_{19}H_{26}O_2$, gave, by the same treatment, a hydrocarbon of much higher m. p. and contrasting ultra-violet spectrum. The latter resembles the spectrum of 4′-methyl-1 : 2-benzfluorene as described by Mayneord and Roe (*Proc. Roy. Soc.*, 1937, *A*, **158**, 634). Although the first attempt to exploit this A ⟶ BCD route has thus broken down, our resources are far from exhausted thereby, and the obvious programme for further work is to attempt the synthesis of a keto-alcohol corresponding to (I) (6-keto-, 3′-hydroxy-).

In this connexion it is of interest that the pressure-hydrogenation of the phenolic ketone (IV) in ethyl acetate solution in the presence of palladised strontium carbonate has afforded a keto-acetate which, on hydrolysis, is changed to a keto-alcohol. The orientation of the carbonyl and the hydroxyl group in this substance or mixture of substances (V, or VI, or both) has not yet been determined.

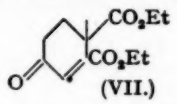
The experimental section contains some additional details relating to the intermediates, including the identification of certain by-products.


(V.)


(VI.)

Two matters not so closely connected with the main series of substances are the following.

The condensation of diethylaminobutanone methiodide with ethyl α-ethoxalylpropionate in the presence of sodium ethoxide might have yielded (VII) which would have been of interest to us. However, the second phase of the process involved loss of the elements of alcohol and the product had the properties of a derivative of dihydroresorcinol (VIII).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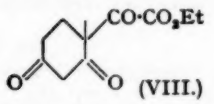
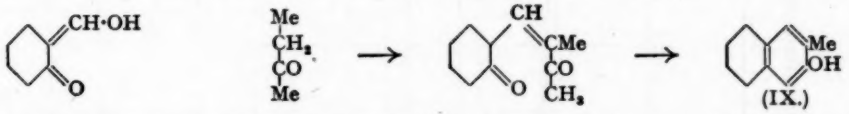

(VIII.)

In Part XLI (*loc. cit.*, p. 493) we described 6-hydroxy-5-methyltetralin, m. p. 113·5—114·5°. It was prepared from 2-methoxy-1-naphthaldehyde by successive hydrogenation and demethylation and therefore the orientation of the substituents seems established.

Parajape, Phalnikar, Bhide, and Nargund (*Rasáyanam*, 1943, **1**, 273) considered that they had obtained the same hydroxymethyltetralin by condensation of 2-hydroxymethylene*cyclo*hexanone with methyl ethyl ketone, followed by treatment of the product with hydrochloric


(IX.)

acid. As their methyltetralol had m. p. 78° it must be an isomeride, and it is almost certainly 6-hydroxy-7-methyltetralin (IX). This is the expected product if the primary condensation involves the methylene group of methyl ethyl ketone.

Experimental.

Degradation of Androstenediols.—Conditions for the reduction of androstenedione, dehydration of the resulting mixture of androstenediols, and finally for dehydrogenation of the product were first established for these substances and used without any modification for the unsaturated ketones $C_{19}H_{26}O_2$. The description given below for the synthetic ketones is therefore applicable.

The main blue-fluorescent band of the chromatogram was separated into 7 fractions by elution with light petroleum (b. p. 60—80°). The middle five fractions crystallised on removal of the solvent and were united and crystallised from methanol. The white, shiny plates had m. p. 115—120° raised to 124—125° (with slight previous sintering) by recrystallisation. The ultra-violet absorption in methanol was found by Dr. F. B. Strauss (Fig. 1) to be almost identical with that of 1 : 2-*cyclo*pentenophenanthrene (cf. Mayneord and Roe, *Proc. Roy. Soc.*, 1935, *A*, **152**, 299). It was probably slightly impure 3′-methyl-1 : 2-*cyclo*pentenophenanthrene.

Some Notes on the Preparation of (IV).—(1) Specimens of methyl oxalate often contain oxalic acid and this has a very deleterious effect on the yield in the methoxalylation stage. (2) The elimination of carbon monoxide from the methoxalyl ketone works best on a relatively small scale and a reduction in the proportion of powdered glass (25—50% of that specified) is advisable. (3) The Reformatzky reaction (*loc. cit.*, p. 494) can be carried out, without diminished yield, with 50 g. of the keto-ester. (4) Arndt–Eistert homologation failed in a series of experiments. This was traced to the use of impure benzene, and the original results (or somewhat better) were obtained when anhydrous "AnalaR" benzene was employed.

Hydrogenation of 6-*Hydroxy*-3′-*keto*-2 : 5-*dimethyl*-1 : 2 : 3 : 4-*tetrahydro*-1 : 2-cyclo*pentenonaphthalene*-a.—The phenolic ketone (a) (10 g.) was hydrogenated in ethyl acetate (120 c.c.) in the presence of palladised strontium carbonate (6 g. of 2%). The conditions were: initially, 18°/105 atms.; after 1½ hours, 215°/156 atms.; after 2½ hours, 220°/146 atms.; after 6½ hours, 228°/131 atms.; after 10 hours, 228°/116 atms. The distilled reaction product was oxidised directly with chromic anhydride (cf. Part XLI, *loc. cit.*). A dark gum, precipitated on the addition of the chromic solution in the cold, had completely disappeared after 5 days at room temperature. The resulting product was isolated in the known manner and distilled. After a very small fraction of lower b. p. three fractions were collected: (*a*) air-bath, 130°/0·1 mm., n_D^{19} 1·4360 (Found: C, 79·9; H, 11·1%); (*b*) air-bath, 135°/0·1 mm., n_D^{19} 1·4530 (Found: C, 74·3; H, 9·6%); (*c*) air-bath, 140°/0·1 mm., n_D^{19} 1·4560 (Found: C, 74·3; H, 9·6; Ac, 17·0. $C_{17}H_{24}O_2$, *keto-acetate*, requires C, 73·3; H, 9·4; Ac, 15·5%). The acetate (fractions *b* and *c*)

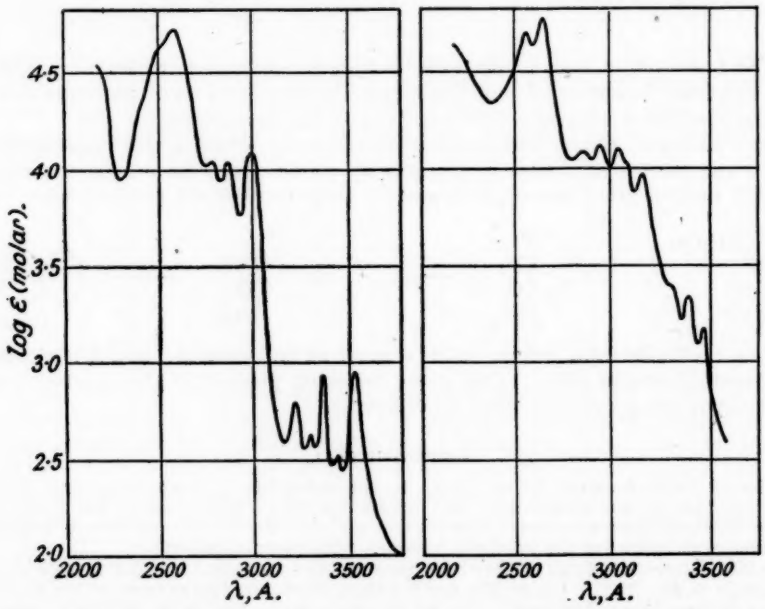
was hydrolysed by means of methanolic potassium hydroxide and the product distilled. The middle fraction (*ca.* 50%), air-bath, 145—150°/0·15 mm., had n_D^{20} 1·5200 (Found: C, 76·3; H, 10·1. $C_{15}H_{24}O_2$ requires C, 76·3; H, 10·2%). All fractions gave sparingly soluble, yellow 2 : 4-dinitrophenylhydrazones.

The condensation of this *keto-alcohol* (V or VI) with 4-diethylaminobutan-2-one methiodide in the presence of alcoholic sodium ethoxide gave, amongst other products, a fraction (separated by repeated chromatographic adsorption and distillation) which on analysis, appeared to be the open-chain *diketone-alcohol* that could be formed (Found: C, 74·4; H, 9·9. $C_{19}H_{30}O_3$ requires C, 74·5; H, 9·9%).

Even on treatment with anhydrous sodium methoxide in boiling benzene under nitrogen this substance did not lose one molecule of water (Found: C, 75·7; H, 10·2%). It is hoped that this material may be further investigated.

Hydrogenation of 3′-*keto*-6-*hydroxy*-2 : 5-*dimethyl*-1 : 2 : 3 : 4-*tetrahydro*-1 : 2-cyclo*pentenonaphthalene*-*a*. The tricyclic ketone (7·5 g.) was hydrogenated in ethanol (125 c.c.) in the presence of Raney nickel (2—3 g.). The conditions were: initially, 20°/115 atms.; after 50 minutes, 180°/160 atms.; after 1½ hours, 204°/162 atms.; after 1¾ hours, 216°/149 atms.; after 2 hours, 214?/138 atms.; after 3 hours, 211°/137 atms. The solvent was removed and an ethereal solution of the product washed with aqueous sodium hydroxide (1·2 g. of alkaline-soluble material, see below). The yield of reduced material was 6·3 g. Despite the use of higher temperatures and longer periods of heating, the hydrogenation could never be brought to completion. The di-*sec.*-alcohol was oxidised with chromic anhydride and the diketone

FIG. 1. FIG. 2.



(*a*) isolated in the known manner (Found: C, 76·9; H, 9·8. Calc. for $C_{15}H_{22}O_2$: C, 76·9; H, 9·4%). A Zerewitinoff determination showed that active hydrogen was absent.

3′ : 6-*Dihydroxy*-2 : 5-*dimethyl*-1 : 2 : 3 : 4-*tetrahydro*-1 : 2-cyclo*pentenonaphthalene*-*a*.—The alkali-soluble material recovered from the above hydrogenation was distilled from an air-bath at 150—160°/0·1 mm. giving a colourless glass (Found: C, 77·6; H, 8·7. $C_{15}H_{20}O_2$ requires C, 77·5; H, 8·7%). This *compound* couples with *p*-nitrobenzenediazonium chloride to an azo-compound which gives a dark violet alkaline solution.

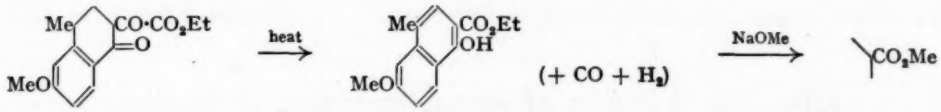
Hydrogenolysis of Methyl 1-*Hydroxy*-2-*carbomethoxy*-6-*methoxy*-2 : 5-*dimethyltetralin*-1-*acetate*.—The hydroxy-dimethyl ester (5 g.) in methanol (120 c.c.) was heated with hydrogen under pressure in the presence of Raney nickel (stirring). The initial conditions were 20°/97 atms. and after 2½ hours at 140—150° the products were isolated by known methods. The *a*-dimethyl ester of 2-carboxy-6-methoxy-2 : 5-dimethyltetralin-1-acetic acid (2·0 g.) was isolated; it had m. p. 110—112° and was identified by comparison with an authentic specimen (cf. Part XLI, *loc. cit.*). The reaction was accordingly simple replacement of hydroxyl by hydrogen.

Treatment of methyl 3′-keto-6-methoxy-2 : 5-dimethyl-1 : 2 : 3 : 4-tetrahydro-1 : 2-*cyclo*pentenonaphthalene-2-carboxylate-*β* with hydriodic acid in hot acetic acid solution afforded, in one experiment, 3′-*keto*-6-*methoxy*-2 : 5-*dimethyl*-1 : 2 : 3 : 4-*tetrahydro*-1 : 2-cyclo*pentenonaphthalene*-*β*. This separated from methanol in stout, white prisms, m. p. 117—118° (Found: C, 78·8; H, 8·4. $C_{16}H_{20}O_2$ requires C, 78·6; H, 8·3%).

Ethyl 6-*Methoxy*-2 : 5-*dimethyl*-1-*tetralone*-2-*carboxylate*.—A mixture of methyl 6-methoxy-2 : 5-dimethyl-1-tetralone-2-carboxylate and ethyl *β*-chloropropionate in benzene–ether was treated with lithium (cf. Nenitzescu and Przematzky, *Ber.*, 1941, **74**, 674). The reaction product was distilled (*ca.* 160°/0·4 mm.). For analysis it was chromatographed on alumina (B.D.H.) from benzene–light petroleum

(b. p. 40—60°). The non-fluorescent (ultra-violet light) material, eluted with benzene, crystallised from benzene–light petroleum (b. p. 40—60°) in colourless prisms, m. p. 58—59° (Found: C, 69·3; H, 7·3. $C_{16}H_{20}O_4$ requires C, 69·5; H, 7·3%). This *ethyl* ester is insoluble in aqueous sodium carbonate and is saturated towards hydrogen (in the presence of a palladium catalyst), potassium permanganate, and bromine. On boiling with a 30% aqueous solution of sodium hydroxide it gave 6-methoxy-2 : 5-dimethyl-1-tetralone (cf. Part XLI). It is therefore probably the ethyl ester corresponding to the starting material. No organo-metallic type of synthesis occurred.

Methyl 1-*Hydroxy*-6-*methoxy*-5-*methyl*-2-*naphthoate*.—The product of methylation of methyl methoxymethyltetralonecarboxylate (cf. Part XLV) was adsorbed after distillation on a column of charcoal from benzene–light petroleum (b. p. 40—60°), and the column washed with pure benzene. The non-fluorescent fraction consisted of pure methylated material and did not give a ferric reaction. The fluorescent material (ultra-violet light) was eluted with ether. It crystallised from methanol in colourless prisms, m. p. 160·5—161·5° (Found: C, 68·2; H, 5·6. $C_{14}H_{14}O_4$ requires C, 68·2; H, 5·7%). The *ester* is insoluble in aqueous sodium carbonate, couples with *p*-nitrobenzenediazonium chloride and diazobenzenesulphonic acid to azo-compounds, and gives a green coloration with ferric chloride in alcoholic solution. On hydrolysis with hot aqueous sodium hydroxide it gave a substance which was soluble in aqueous sodium carbonate. The most likely constitution is that given above and it is considered to owe its formation to dehydrogenation during the thermal decomposition of the ethoxalylketone:



The Mixed Unsaturated Ketones, $C_{18}H_{26}O_2$.—The penultimate stage was carried out as described in Part XLI (*loc. cit.*, p. 497) and led to stereoisomerides of 3′ : 6-diketo-2 : 5-dimethyldecahydro-1 : 2-*cyclo*pentenonaphthalene-α. The following modification was used for the last stage. A mixture of the diketones (2 g., not crystallised), powdered sodamide (2 g.) and ether (50 c.c.) was refluxed for 6 hours under nitrogen, then cooled in ice while a solution of 4-diethylaminobutan-2-one methiodide (from 2 g. of the base) in alcohol (25 c.c.) was slowly introduced (1½ hours). After another 1½ hours in ice, the mixture was kept at room temperature for 14 hours and finally refluxed for 45 minutes. The ethereal extract was distilled. The fraction boiling above 180°/0·1 mm. (air-bath) was redistilled, and the fraction of b. p. 180—190°/0·1 mm. (air-bath) chromatographed from benzene–light petroleum (b. p. 40—60°) (1 : 2). The main bluish-green fluorescent band (ultra-violet light) was eluted with pure benzene and distilled (air-bath) at 190—200°/0·1 mm. (Found: C, 79·8; H, 9·1. Calc. for $C_{19}H_{26}O_2$: C, 79·7; H, 9·2%). The absorption in alcoholic solution (c, 1·297 $\times 10^{-4}$) examined by Dr. F. B. Strauss showed $\lambda_{max.}$, 2420 A.; $\varepsilon_{max.}$, 11,780; log $\varepsilon_{max.}$, 4·071; $\varepsilon_{max.}$, 1·528 (cf. Part XLV).

Degradation.—Sodium (10 g.) was added in small portions to a boiling solution of the ketones (0·9 g.), the combined product from a number of condensations (Found: C, 79·3; H, 9·1%) in *n*-propyl alcohol (175 c.c.). When all the sodium had disappeared, water was added and the solution neutralised with acetic acid. The alcohol was removed and the residue extracted with ethyl acetate. The organic layer was washed with aqueous sodium carbonate and water, and dried. The reduction product (0·9 g.) did not react with Brady's reagent.

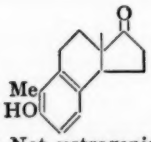
It was dehydrated by heating for an hour at 180° with fused potassium hydrogen sulphate (2·5 g.). The product (0·65 g.) was then dehydrogenated by selenium (1·5 g.) during 26 hours at 320—340°. A benzene solution of the reaction product was passed through a very short column of charcoal. The solvent was removed, the residue adsorbed on alumina (B.D.H.) from light petroleum (b. p. 60—80°), and the column washed with pure light petroleum (b. p. 60—80°). The main blue-fluorescent band (ultra-violet light) was thus separated into three fractions (A, B, C) and by washing with pure benzene another fraction was obtained (D). These four fractions were rechromatographed separately and yielded 8—10 fractions each. No crystalline fractions were obtained from (A). The two middle fractions from (B) crystallised on removal of the solvent. One of the middle fractions from (C) also crystallised. None of the fractions from (D) could be induced to crystallise. The crystalline fractions from (B) and (C) were sublimed separately at 120°/0·1 mm. and shown to be identical by their absorption spectrum. They were therefore combined and crystallised from methanol. The substance separated in glistening, white plates, m. p. 175—180° raised to 190—198° after recrystallisation. Insufficient material was available for further purification. The absorption in ether of this substance (m. p. 190—198°) was examined by Dr. F. B. Strauss and shows clearly that it is a derivative of 1 : 2-benzfluorene (probably 4′-methyl-1 : 2-benzfluorene) (cf. Fig. 2 and Mayneord and Roe, *loc. cit.*). A thorough search for other crystalline hydrocarbons in the dehydrogenation product failed.

Ethyl 2 : 4-*Diketo*-1-*methyl*cyclo*hexane*-1-*glyoxylate* (VIII).—A solution of sodium ethoxide (2·5 g. of sodium) in anhydrous alcohol (50 c.c.) and benzene (25 c.c.) was added dropwise in an atmosphere of nitrogen to a well-stirred solution of ethyl ethoxalylpropionate (20·2 g.; *Org. Synth.*, 1937, **17**, 54) in benzene (30 c.c.). 4-Diethylaminobutan-2-one methiodide (from 15 g. of the base) in absolute alcohol (50 c.c.) was added gradually to the above ice-cooled solution. The mixture was kept in ice for 2 hours and at room temperature overnight. A further solution of sodium ethoxide (2 g. of sodium) in alcohol (25 c.c.) was added, and the mixture kept for two days at the room temperature. The solution was poured on ice and hydrochloric acid and extracted with ether. The ethereal solution was washed with aqueous sodium hydrogen sulphite, aqueous sodium carbonate, and water. Distillation of the product gave: (i) b. p. 105—109°/9 mm.; (ii) b. p. 150°/0·6 mm. The second fraction on redistillation gave a very pale yellow oil, b. p. 138—140°/0·5 mm. (Found: C, 58·4; H, 6·5. $C_{11}H_{14}O_5$ requires C, 58·4; H, 6·2%).

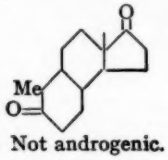
With ferric chloride in methanol this *diketo*-ester gave a dark brown-red coloration. On treatment

of an alcoholic solution with semicarbazide acetate an intense red colour developed and a yellow solid soon separated, m. p. 195—198° (decomp.). It crystallised from methanol in almost colourless crystals, m. p. 198—201° (decomp.) to a red liquid (Found: C, 50·9; H, 6·0. $C_{12}H_{17}O_5N_3$ requires C, 50·9; H, 6·0%). This *semicarbazone* gave a violet coloration with ferric chloride in methanol.

Biological Tests.—



(β) Not œstrogenic.



(α) Not androgenic.

Unsaturated ketones, $C_{19}H_{26}O_2$ (α). Not androgenic.

We wish to thank Mr. F. Hastings for help in the preparation of some of the starting materials, and Imperial Chemical Industries Ltd. for financial assistance. We are also indebted to Prof. E. C. Dodds, F.R.S., for biological tests.

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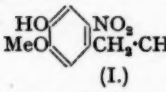
398. *The Nitration of Some Derivatives of Eugenol.*

By G. R. CLEMO and J. H. TURNBULL.

6-*Nitroeugenol* has been prepared and orientated by degradation to the known 6-nitrohomovanillic and 6-nitrohomoveratric acids.

5-NITROEUGENOL is known (Weselsky and Benedict, *Monatsh.*, 1883, **3**, 386; Klemenc, *ibid.*, 1912, **33**, 378; Levin and Lowy, *J. Amer. Chem. Soc.*, 1933, **55**, 1995), but the isomeric 6-nitro-compound has not hitherto been described. 6-*Nitroeugenol* (2-*nitro*-4-*hydroxy*-5-*methoxy*-*allylbenzene*) (I) is an intermediate in the preparation of the interesting 6-nitrohomovanillin, and is now easily accessible from eugenol. Nitration of eugenyl acetate, followed by hydrolysis, gave a poor yield of (I); it is more conveniently obtained by the nitration of *O*-benzyleugenol, to give 6-*nitro*-O-*benzyleugenol*, from which the benzyl group is then removed.



(I.)

Nitration of methyleugenol yields 6-*nitro*-O-*methyleugenol*, which is also prepared by the methylation of (I).

The position of the nitro-group in the nitro-compounds has been established by oxidation. 6-*Nitroeugenyl acetate* is oxidised by weakly acid permanganate solution to 6-nitrohomovanillic (2-nitro-4-hydroxy-5-methoxyphenylacetic) acid, whereas 6-*nitro*-O-*methyleugenol* yields 6-nitrohomoveratric (2-nitro-4 : 5-dimethoxyphenylacetic) acid and 6-nitroveratraldehyde on oxidation under similar conditions.

EXPERIMENTAL.

6-*Nitroeugenol*.—To eugenyl acetate (3·2 g.) in acetic anhydride (6 c.c.) a cold mixture of acetic anhydride (7 c.c.) and nitric acid (2·01 g.; sp. gr. 1·49) was added during 30 minutes with stirring. After 4 hours the product was poured into water and extracted with ether, the extracts were washed with water and sodium hydrogen carbonate solution and dried (Na_2SO_4), and the ether removed. The residue was dissolved in methanol (10 c.c.), a cool solution of potassium hydroxide (1·3 g.) in methanol (30 c.c.) added, and the mixture shaken for 5 hours, poured into water, and saturated with carbon dioxide. The product was extracted with ether, the extracts were washed (water) and dried, the ether was removed, and the 6-*nitroeugenol* distilled in a vacuum, giving a yellow oil, b. p. 150—160°/2 mm., which solidified to a waxy solid and crystallised from light petroleum (b. p. 40—60°) as white needles (0·3 g.), m. p. 69—71° (Found: C, 57·5; H, 5·6. $C_{10}H_{11}O_4N$ requires C, 57·4; H, 5·4%). It gave an intense red solution in concentrated sulphuric acid.

6-*Nitroeugenyl Acetate*.—6-Nitroeugenol (0·6 g.) was dissolved in pyridine (1 c.c.) and acetic anhydride (0·5 g.), and acetyl chloride (0·5 g.) was added dropwise at 0°. The mixture was kept for 10 minutes at room temperature and then diluted with water. The *acetate* separated and slowly solidified; it crystallised from methanol in large colourless plates (0·5 g.), m. p. 92—94° (Found: C, 57·6; H, 5·1. $C_{12}H_{13}O_5N$ requires C, 57·4; H, 5·2%).

6-*Nitro*-O-*benzyleugenol*.—Benzyleugenol (3·5 g.) (*Chem. Zentr.*, 1937, II, 3452) was dissolved in glacial acetic acid (21 c.c.), and a mixture of nitric acid (1·9 g.; sp. gr. 1·42) and acetic acid (5·2 c.c.) was added dropwise during 20 minutes at 9—11°. After a further 1·5 hours at 9—11° the product was poured into water and extracted with ether, the extracts were washed repeatedly with water and sodium hydroxide solution (5%) and dried (Na_2SO_4), and the ether removed. The *nitro*-compound slowly crystallised (3·0 g.) (m. p. 49—53°) and recrystallised from light petroleum (b. p. 40—60°) in long pale-yellow needles (1·9 g.), m. p. 58—59° (Found: C, 67·9; H, 5·7. $C_{17}H_{17}O_4N$ requires C, 68·2; H,

5·7%). The substance was insoluble in sodium hydroxide and gave an intense red solution in concentrated sulphuric acid.

6-Nitroeugenol.—6-Nitro-*O*-benzyleugenol (0·8 g.) was dissolved in warm glacial acetic acid (8 c.c.), concentrated hydrochloric acid (6 c.c.) added, and the mixture boiled gently under reflux for 10 minutes. The solution was diluted with water, benzyl chloride removed in a current of steam, and the residual solution cooled, whereupon an oil separated; this solidified (0·45 g.; m. p. 58—63°) and was distilled at 2 mm. (bath-temperature, 190°). The distillate solidified and was recrystallised from light petroleum (b. p. 40—60°), to give white needles (0·27 g.), m. p. 69—71°, not depressed by admixture with authentic 6-nitroeugenol.

6-Nitro-O-methyleugenol.—(*a*) Methyleugenol (3 g.) was mixed with glacial acetic acid (12 c.c.), and nitric acid (2·4 g.; sp. gr. 1·42) was added dropwise at 5—8° during 20 minutes. After 3 hours the product was poured into water and worked up as in the experiment with benzyleugenol, to give *6-nitro-O-methyleugenol* as a yellow solid (1·9 g.), m. p. 38—40°, which crystallised from light petroleum (b. p. 40—60°) in pale yellow prisms, m. p. 41—43°, soluble in concentrated sulphuric acid to give an intense-red solution (Found: C, 59·8; H, 5·7. $C_{11}H_{13}O_4N$ requires C, 59·2; H, 5·8%).

(*b*) 6-Nitroeugenol (100 mg.) was dissolved in N-sodium hydroxide solution (3 c.c.), methyl sulphate (80 mg.) added, and the mixture shaken for 30 minutes. An oil separated and slowly crystallised (55 mg.; m. p. 39—41°). Recrystallisation from light petroleum gave pale yellow prisms, m. p. 41—43°, identical with 6-nitromethyleugenol (above). Unmethylated 6-nitroeugenol (20 mg.) was recovered.

Oxidation of 6-Nitroeugenyl Acetate.—6-Nitroeugenyl acetate (0·6 g.) was suspended in a hot mixture of water (240 c.c.) and glacial acetic acid (0·6 c.c.), and a solution of potassium permanganate (1·4 g.) in hot water (120 c.c.) was gradually added at 70—80° during 2 hours with frequent shaking. The permanganate was rapidly decolorised. The solution was filtered, basified (sodium hydroxide) evaporated to small bulk, and acidified (hydrochloric acid); 6-nitrohomovanillic acid then separated and crystallised from water (charcoal) in pale yellow needles (0·2 g.), m. p. 165—167° after sintering at 110°; it melted at 180° after drying for 4 hours at 100° (Found: C, 47·6; H, 3·9. Calc. for $C_9H_9O_6N$: C, 47·6; H, 4·0%). Gulland (*J.*, 1931, 2897) records m. p. 170°, sinters at 110°, and m. p. 184° after drying at 100°.

Oxidation of 6-Nitromethyleugenol.—6-Nitro-*O*-methyleugenol (1 g.) was suspended in hot water (500 c.c.) containing acetic acid (1·1 g.), and a hot solution of potassium permanganate (2·7 g.) in water (225 c.c.) added gradually at 70—80° during 2 hours with occasional shaking. The solution was filtered, basified (sodium hydroxide), and evaporated to small bulk, whereupon a solid (*A*) separated. When the filtrates were acidified, 6-nitrohomoveratric acid separated; this crystallised from water (charcoal) in long glistening pale yellow needles (0·3 g.), m. p. 201—203° (Found: C, 50·0; H, 4·5. Calc. for $C_{10}H_{11}O_6N$: C, 49·8; H, 4·6%). Gulland (*loc. cit.*) records m. p. 206°.

The solid (*A*) was crystallised from alcohol, to give pale yellow needles which became bright yellow in sunlight and had m. p. 131—132°, not depressed by admixture with authentic 6-nitroveratraldehyde (Pschorr, *Ber.*, 1899, **32**, 3412).

6-Nitrohomoveratric Acid.—6-Nitrohomovanillic acid, prepared as above, was methylated according to the method of Gulland (*loc. cit.*) and yielded 6-nitrohomoveratric acid, m. p. 200—202°, identical with the specimen prepared by the oxidation of 6-nitromethyleugenol.

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399. *The Kinetics and Mechanism of Sulphonation in Sulphuric Acid.*

By W. A. COWDREY and D. S. DAVIES.

The kinetics of the sulphonation of *p*-nitrotoluene have been measured over the range 92% sulphuric acid to 10% oleum, where there is no significant reverse reaction. The rate is proportional to the concentrations of nitrotoluene and of sulphur trioxide [which in 92—99% acid is proportional to $1/w(w + c)$, where w and c are the respective analytical contents of water and added sodium hydrogen sulphate].

The true activation energy is 7·4 kcals. in sulphuric acid and 18·0 kcals. in oleum.

These facts suggest that the reaction is a simple bimolecular attack of sulphur trioxide on nitrotoluene, the disposal of the displaced proton being more difficult in oleum, and this is discussed in terms of the assumption that sulphuric acid is a hydrogen-bonded liquid like water.

This mechanism provides a semi-quantitative explanation for previously recorded rates of sulphonation and desulphonation.

AROMATIC sulphonation is almost certainly brought about by an electron-seeking or " kationoid " reagent (cf. Robinson, " Outline of an electrochemical theory of organic reactions," Inst. of Chem., 1932; Ingold, *Chem. Reviews*, 1934, **15**, 225); the precise nature of the attacking species, and the mode of disposal of the displaced proton, are, however, unknown. Recent investigations on nitration in sulphuric acid (Kharasch and Westheimer, *J. Amer. Chem. Soc.*, 1946, **68**, 1871; Ingold, Hughes, *et al.*, *Nature*, 1946, **158**, 448, 480, 514; Bennett *et al.*, *J.*, 1946, 869, 875; 1947, 474) have shown that here the reaction is brought about by the ion NO_2^+ and that the proton is

removed by HSO_4^-, H_2SO_4, or $HS_2O_7^-$. The present paper describes a parallel investigation designed to establish which of the species SO_3, SO_3H^+, H_2SO_4, or $(SO_3)_n$ is the sulphonating agent in sulphuric acid, and to discover the fate of the hydrogen ion.

Previous experimental work on the kinetics of sulphonation in sulphuric acid is sketchy. Martinsen (*Z. physikal. Chem.*, 1908, **62**, 713) followed the sulphonation of *p*-nitrotoluene in 99·4% and 100% sulphuric acid and in 2·4% oleum by a method depending on the differing ease of nitration of reactant and product, but neither he nor Joffe (*J. Gen. Chem. U.S.S.R.*, 1933, **3**, 437) could adequately explain the results. The results obtained in oleum can approximately be represented by an equation for a reaction of first order; Martinsen interpreted the reaction as being of the first order with respect to nitrotoluene and of zero order with respect to sulphur trioxide, whilst Joffe preferred to regard it as of the first order with respect to both; the experimental results barely permit a decision between the two. Neither author could explain the results in sulphuric acid, where the reaction was very much slower and retarded by the water produced, so that the order could not be determined. Pinnow (*Z. Elektrochem.*, 1915, **21**, 380; 1917, **23**, 243) measured the rate of the reversible sulphonation of quinol in 40—70% sulphuric acid. The forward reaction was of the first order with respect to quinol, and the back reaction was of the first order with respect to the sulphonic acid. Both rates increased with the concentration of sulphuric acid, the former more sharply than the latter. No satisfactory conclusions about the mechanism were drawn. Lauer and Oda (*J. pr. Chem.*, 1935, **144**, 32) studied the kinetics of anthraquinone sulphonation in oleum, but they worked always at equimolecular concentrations of anthraquinone and sulphur trioxide. The ratio (initial rate/anthraquinone concentration) increased with the sulphur trioxide concentration over the range 1—6% and then dropped almost to zero, finally increasing again between 10% and 20%, and they postulated that sulphur trioxide in 5—10% oleum was in an "inactive" form.

A study of sulphonation, in nitrobenzene, by sulphur trioxide and sulphuric acid was made by Hinshelwood and his collaborators (*J.*, 1939, 1372; 1944, 469, 649). The reaction is first-order with respect to the aromatic compound and second-order with respect to sulphur trioxide, and the latter dependence was interpreted as meaning either that S_2O_6, present in small concentration, is the sulphonating agent, or that one molecule of SO_3 is required as sulphonating agent and another to remove the displaced proton. The activation energies in the sulphonation of a series of substituted benzene derivatives are linearly related to the dipole moments (or algebraic sum of the group moments.)

In the present investigation, the kinetics of sulphonation of *p*-nitrotoluene (chosen for analytical convenience) have been measured in 92—99% sulphuric acid and 1—8% oleum at a series of temperatures.

Experimental.

Oleum solutions were prepared by drawing dry air through warm 65% oleum and into 98% AnalaR sulphuric acid, and standardised by the method of Brand (*J.*, 1946, 585). The end-point of each titration was checked by determining the final freezing point of the acid, and, if necessary, a small correction was made.

100% Sulphuric acid was prepared by mixing pure oleum with 98% AnalaR sulphuric acid in proportions such that the m. p. was 10·4°, it being assumed (cf. Brand, *loc. cit.*) that acid of maximum m. p. is 100% in concentration.

Kinetics of Nitrotoluene Sulphonation in 92—99% *Sulphuric Acid.*—These were measured by making up solutions of weighed quantities of nitro-compound, water, and dried anhydrous sodium sulphate in 100% sulphuric acid, and heating aliquot samples in sealed tubes immersed in constant-temperature baths for known times. Reaction was stopped by cooling, and the samples were diluted with water and extracted with benzene to remove unchanged nitrotoluene. The nitrotoluenesulphonic acid was determined by adding an excess of standard titanous sulphate, boiling under carbon dioxide, and back-titrating with standard ferric alum.

Kinetics of Sulphonation in Oleum.—These were determined by making up, by weight, a solution of nitrotoluene in 100% sulphuric acid in a vessel provided with a side-arm, connected through a ground joint, and containing a weighed quantity of oleum of known strength. The apparatus was immersed in a thermostat, and the two solutions were mixed by rotating the side-arm in the ground joint. At intervals samples were removed with a pipette, and the reaction was stopped by drowning into water. Analysis was carried out as before. "Blank" experiments showed that no significant absorption of water occurred during these operations. No attempt to maintain a constant ionic strength was made, for two reasons. First, the use of perchlorates (the only salts which could be used) in reactions in sulphuric acid at *ca.* 100° does not seem desirable; secondly, sulphuric acid is a solvent in which salt effects are likely to be small (cf. Hammett, "Physical Organic Chemistry," McGraw Hill, 1940, p. 278).

Results in 92—99% *Sulphuric Acid.*—The reaction is a simple first-order process as long as the water produced does not seriously change the total water concentration. The apparent rate constant is depressed by increasing the analytical water content w or by adding sodium hydrogen sulphate (concentration, c moles/l.), and is proportional to $1/w(w + c)$.

The true rate equation is therefore :

$$-\mathrm{d}[p\text{-nitrotoluene}]/\mathrm{d}t = k[p\text{-nitrotoluene}]/w(w + c) \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where w includes the water produced during sulphonation.

Thus,
$$\mathrm{d}x/\mathrm{d}t = \frac{k(a - x)}{(b + x)\ (b + c + x)},$$

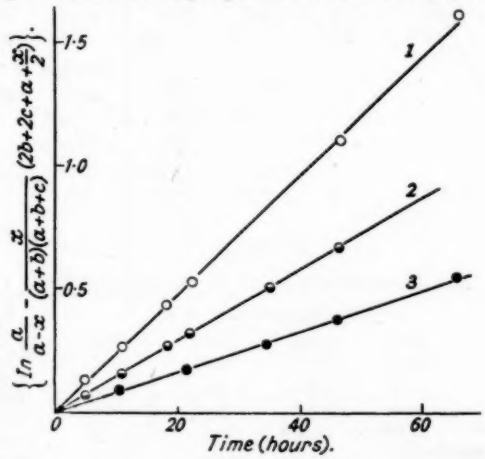
where a = [p-nitrotoluene] initial, $b = [w]_{\text{initial}}$, c = [HSO_4^-] added, and x = [sulphonic acid] at time t. This gives, on integration,

$$kt = (a + b)\ (a + b + c)\left[\ln\frac{a}{a - x} - \frac{x}{(a + b)(a + b + c)}\ (2b + 2c + a + 0{\cdot}5\ x)\right]$$

Typical experimental data are given in Table I, and test plots of t against the quantity in square brackets are shown in Fig. 1.

FIG. 1.

Sulphonation of p-*nitrotoluene in* H_2SO_4 *at* 96·5° : *lines showing course of reaction.*



	a ([p.n.t.]$_{\text{initial}}$).	b $[w]_{\text{initial}}$.	c ([HSO_4^-] added).
1.	0·2	1·47	0
2.	0·2	1·47	0·906
3.	0·2	1·47	2·615

TABLE I.

Analytical data for runs at 96·5° *in sulphuric acid containing water and* HSO_4^-.

The concentration, x, of p-nitrotoluenesulphonic acid is given as the number of c.c. of ferric alum solution equivalent to the sulphonic acid in a 10-c.c. portion of the sulphonation mixture.

Run 1. b = 1·47, c = 0, a = 0·200 mole/l. See Fig. 1.

t (hr.)	0	5·25	11·25	18·4	22·5	46·8	66·4				k = 0·067
x (0·206M.)	0	8·25	16·2	23·7	27·5	41·7	48·75				

Run 2. b = 1·47, c = 0·906, a = 0·200. See Fig. 1.

t (hr.)	0	5·1	11·1	18·35	22·35	35·1	46·7				k = 0·061
x (0·206M.)	0	5·1	10·5	16·3	19·1	26·6	32·05				

Run 3. b = 1·47, c = 2·615, a = 0·200. See Fig. 1.

t (hr.)	0	10·67	21·8	34·67	46·25	65·8					k = 0·059
x (0·206M.)	0	6·6	11·5	17·0	21·7	28·0					

Run 4. b = 3·19, c = 0, a = 0·200.

t (hr.)	0	17·0	24·2	41	47·7	64·8	70·7	90·3	112·7	208·7	k = 0·073
x (0·204M.)	0	7·0	8·9	14·6	17·0	22·2	23·9	27·3	31·15	45·25	

Run 5. b = 5·51, c = 0, a = 0·200.

t (hr.)	0	64·5	111·75	136·5	160·5	207·5	259·5	351·5	472·5		k = 0·067
x (0·204M.)	0	8·7	12·5	15·8	17·1	22·1	24·6	31·0	36·8		

The slopes of these lines (apparent rate constants) for different runs at 96·5° are plotted against $1/(a + b)(a + b + c)$ in Fig. 2; again the relation is linear. The rate constant k of equation (i) (in g.-mol.$^{\frac{1}{2}}$l.$^{-\frac{1}{2}}$hr.$^{-1}$) is equal to the slope of this line and is 0·066 hr.$^{-1}$ at 96·5°. Values of k from individual runs at four temperatures are shown in Table II. It will be noticed that k falls when w falls below 1·4M.;

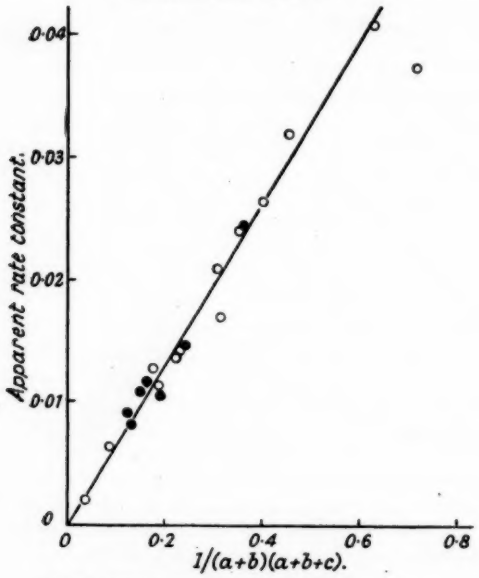
this effect is most apparent at the lower temperatures, where the higher water concentrations cannot be used, as the rate becomes too small. In obtaining mean values for k, rates at values of w less than 1·0 have been disregarded.

The mean values obey the Arrhenius law, and correspond to an activation energy of 27·4 ± 0·3 kcals. per mole.

Under the conditions of these experiments, the reverse reaction (desulphonation of nitrotoluenesulphonic acid) was shown by experiment to be negligible.

FIG. 2.

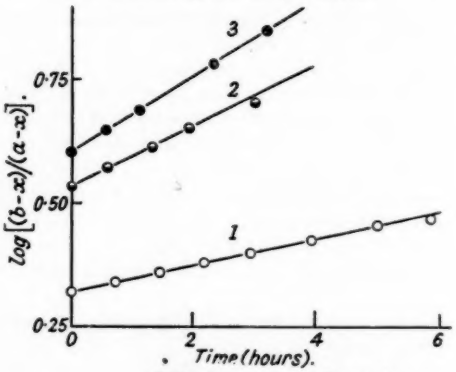
Effect of H_2O *and* HSO_4^- *on rate of* p-*nitrotoluene sulphonation at* 96·5°.



Open circles: water alone added.
Full circles: water and bisulphate added.

FIG. 3.

Sulphonation of p-*nitrotoluene by oleum at* 25°: *lines showing course of reaction.*



	$[SO_3]_{initial.}$	$[p.n.t.]_{initial.}$
1.	0·385	0·136
2.	0·685	0·199
3.	1·270	0·182

Results in Oleum.—Here the reaction is a simple bimolecular process of the first order with respect to both p-nitrotoluene and free sulphur trioxide (initial concentration d g.-mols.l.$^{-1}$). A few typical experimental results and second-order plots are shown in Table III and Fig. 3. The full list of rate constants k_2(g.-mol.l.$^{-1}$hr.$^{-1}$) obtained at three temperatures is given in Table IV.

TABLE II.

Rate constants for sulphonation in < 100% *sulphuric acid.*

a, b, and c are given in mol.l.$^{-1}$

	b.	a.	c.	k.		b.	a.	c.	k.
At 96·5°.	5·51	0·2	—	0·067	At 70·5°.	2·24	0·2	—	0·0039
	3·19	0·2	—	0·074		1·78	0·2	—	0·0030
	2·32	0·2	—	0·073		1·33	0·2	—	0·0032
	1·92	0·2	—	0·062		1·05	0·2	—	0·0028
	1·59	0·2	—	0·068		[0·78	0·2	—	0·0023]
	1·38	0·4	—	0·054				Mean	0·0032$_3$
	1·38	0·2	—	0·066					
	1·38	0·1	—	0·070					
	[0·98	0·2	—	0·052]	At 80·5°.	2·73	0·2	—	0·0120
	2·17	0·2	—	0·072		2·24	0·2	—	0·0115
	2·17	0·2	0·195	0·072		1·78	0·2	—	0·0102
	2·17	0·2	0·395	0·072		1·365	0·2	—	0·0092
	2·17	0·2	0·998	0·073		1·14	0·2	—	0·0086
	1·47	0·2	—	0·067		[0·81	0·2	—	0·0065]
	1·47	0·2	0·906	0·061				Mean	0·0103
	1·47	0·2	2·615	0·059					
	1·061	0·2	—	0·065					
	1·061	0·2	0·927	0·067	At 117°.	5·5	0·2	—	0·045
	1·061	0·2	1·998	0·060					
	1·061	0·2	2·845	0·057					
			Mean	0·066					

TABLE III.

Analytical data for sulphonation in oleum.

For value of x see Table I.

Run 6. 13·5°. $a = 0·217$, $d = 0·438$.									
Time (hr.)	0	2·4	4·7	6·27	8·8	10·4			$k_2 = 0·085$
x (0·200M.)	0	5·45	9·9	12·7	16·6	18·9			
Run 1. 25°. $a = 0·182$, $d = 1·27$ moles/l. See Fig. 3.									
Time (hr.)	0	0·24	0·49	0·75	1·07	1·52	3·0	5·8	$k_2 = 0·34$
x (0·201M.)	0	7·1	10·3	14·7	19·6	25·7	37·2	46·0	
Run 2. 25°. $a = 0·199$, $d = 0·685$. See Fig. 3.									
Time (hr.)	0	0·56	1·27	1·89	2·96				$k_2 = 0·30$
x (0·201M.)	0	6·9	13·3	18·5	24·4				
Run 3. 25°. $a = 0·186$, $d = 0·385$. See Fig. 3.									
Time (hr.)	0	0·71	1·44	2·17	2·92	3·92	5·0	5·83	21·58 $k_2 = 0·31$
x (0·201M.)	0	5·25	8·6	12·2	15·4	19·1	22·6	24·7	43·4
Run 4. 40°. $a = 0·212$, $d = 0·945$.									
Time (hr.)	0	0·14	0·35	0·51	0·87				$k_2 = 1·54$
x (0·197M.)	0	10·7	25·3	32·5	43·5				
Run 5. 40°. $a = 0·216$, $d = 0·343$.									
Time (hr.)	0	0·325	0·65	1·15	1·67				$k_2 = 1·42$
x (0·201M.)	0	8·7	15·3	23·4	30·0				

TABLE IV.

Rate constants for sulphonation in oleum.

$a = 0·2$ throughout.

At 40°.	d	0·34	0·53	0·81	0·95	0·95	0·98	1·16	1·51
	k_2	1·42	1·31	1·66	1·54	1·50	1·41	1·51	1·62
At 25°.	d	0·21	0·39	0·69	0·82	1·12	1·27		
	k_2	0·30	0·31	0·30	0·31	0·34	0·34		
At 13·5°.	d	0·44	0·75	0·98	1·09	1·71	2·16		
	k_2	0·085	0·094	0·080	0·110	0·120	0·143		

The activation energy derived from these values is 18·0 kcals. per mole, and the non-exponential (A) factor in the Arrhenius equation is $1·6 \times 10^9$ g.-mol.l.$^{-1}$sec.$^{-1}$.

The rate constant shows definite signs of increasing when the sulphur trioxide concentration is high (>1) and most markedly at the lowest temperature (13·5°); this may be due to the existence of an additional reaction of higher order in sulphur trioxide.

Discussion.

A mechanism of sulphonation is required consistent with the facts that the rate of sulphonation is proportional to $[RH]/w(w + c)$ (activation energy, 27·4 kcals.) in 92—99% sulphuric acid and to $[SO_3][RH]$ (activation energy, 18·0 kcals.) in oleum.

The sulphonating agents which have been considered are SO_3, HSO_3^+, S_2O_6, or H_2SO_4. Possible proton-acceptors are HSO_4^-, H_2SO_4, SO_3, or $HS_2O_7^-$. The species undergoing sulphonation is almost certainly the unchanged nitro-compound; Hammett and Deyrup (*loc. cit.*) have shown that RNO_2H^+ formation is small in 100% sulphuric acid; this (and $RNO_2{\cdot}SO_3$) will sulphonate more slowly than RNO_2, and the presence of these complexes in minor proportions will be unimportant.

The concentration of the various possible reactant species can be calculated in terms of the stoicheiometric concentrations of water (w) or added HSO_4^- (c) in sulphuric acid of less than 100% strength (which, for convenience, we shall call " vitriol " in the rest of this discussion), or of sulphur trioxide (d) in oleum. Hammett and Deyrup (*J. Amer. Chem. Soc.*, 1933, **55**, 1900) have shown that the equilibrium, $H_2O + H_2SO_4 \rightleftharpoons OH_3^+ + HSO_4^-$, lies almost completely to the right in concentrated sulphuric acid, *i.e.*, water is a strong base in sulphuric acid.

Hence, dissociation of sulphuric acid into sulphur trioxide or HSO_3^+ will occur according to the equations:

$$2H_2SO_4 \rightleftharpoons SO_3 + OH_3^+ + HSO_4^- \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$3H_2SO_4 \rightleftharpoons HSO_3^+ + OH_3^+ + 2HSO_4^- \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

(equilibrium constants, respectively, K_1 and K_2)

Since one mole of water gives rise to one mole each of OH_3^+ and HSO_4^-, and HSO_4^- dissolves unchanged, in 92—99% sulphuric acid the various concentrations are

$$\begin{aligned}
[SO_3] &= K_1/w(w+c)\\
[HSO_3^+] &= K_2/w(w+c)^2\\
[S_2O_6] &= K_1^2K_3/w^2(w+c)^3 \ (K_3 \text{ being the constant for } SO_3 \text{ dimerisation})\\
[HSO_4^-] &= w+c\\
[HS_2O_7^-] &= K_2K_1/w
\end{aligned}$$

In oleum, the following equilibria are important

$$SO_3 + HSO_4^- \rightleftharpoons HS_2O_7^- \quad \ldots\ldots\ldots\ldots \quad (4)$$

$$SO_3 + 2H_2SO_4 \rightleftharpoons H_3SO_4^+ + HS_2O_7^- \quad \ldots\ldots\ldots \quad (5)$$

$$2SO_3 + H_2SO_4 \rightleftharpoons HSO_3^+ + HS_2O_7^- \quad \ldots\ldots\ldots \quad (6)$$

(equilibrium constants, respectively, K_4, K_5, and K_6.)

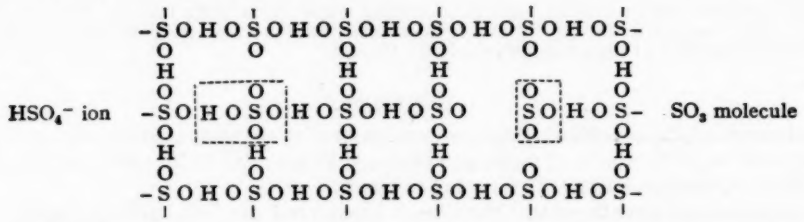
In (4), equilibrium is predominantly to the right (cf. Brand, *J.*, 1946, 880); in (5) and (6), it is predominantly to the left, since the addition of sulphur trioxide to sulphuric acid brings about only a small rise in conductivity.

Thus,

$$\begin{aligned}
[SO_3] &= d\\
[HSO_3^+] &= K_6/\sqrt{(K_6d^2 + K_5d)}\\
[HS_2O_7^-] &= \sqrt{(K_6d^2 + K_5d)}\\
[HSO_4^-] &= \sqrt{K_6d^2 + K_5d}/K_4d = \sim 0, \text{ as } K_6 \text{ and } K_5 \text{ are small and } K_4 \text{ is large.}
\end{aligned}$$

It is assumed that an acceptable mechanism is one in which the product of the concentrations of sulphonating agent and proton-acceptor depends on the same functions of medium concentration as does the rate of reaction. This condition is only fulfilled by the combinations, SO_3/H_2SO_4 and HSO_3^+/HSO_4^-.

Although these represent formally different mechanisms, it is doubtful whether there is any physical distinction between them, for the following reason. Sulphuric acid, like water (Bernal and Fowler, *J. Chem. Phys.*, 1933, **1**, 515), almost certainly has a hydrogen-bonded structure in the liquid state; it has a high dielectric constant and, as in water, the hydrogen ions are exceptionally mobile (Hammett and Lowenheim, *J. Amer. Chem. Soc.*, 1934, **56**, 2620). Sulphur trioxide and HSO_4^- will not exist as independent entities, but will be incorporated in the lattice and there constitute a kind of lattice defect. A typical micro-crystalline region containing these defects might schematically be represented as follows:



In the critical act of sulphonation, the two species responsible for substitution and proton removal are likely to be hydrogen-bonded together, either directly or through a solvent molecule. The difference, therefore, between mechanisms involving (*a*) SO_3 and H_2SO_4 or (*b*) HSO_3^+ and HSO_4^- depends upon the assignment of a proton involved in an O—H—O bond to one or other of the bound oxygen atoms, and such a distinction may lack physical justification. In the rest of this discussion the SO_3/H_2SO_4 formulation is used; the arguments apply with equal force to the HSO_3^+/HSO_4^- mechanism.

There remains for consideration the connection between the rate constants in vitriol and in oleum. If the true rate constant k_1 for the SO_3/RH reaction were the same in both cases, then, since the apparent rate constant in concentrated sulphuric acid is k_1K_1 and that in oleum is k_1, the quotient at a given temperature should be equal to the equilibrium constant K_1, and the difference in apparent activation energies to the heat, ΔH_1, of the reaction

$$2H_2SO_4 \rightleftharpoons SO_3 + OH_3^+ + HSO_4^-.$$

Although K_1 is not known and no method for its determination is readily available, ΔH_1 (which is simply the heat of reaction of one mole of water with one mole of sulphur trioxide,

both dissolved in an infinite amount of sulphuric acid) has been found to be 20·0 kcals. per mole (Miles, Niblock, and Smith, *Trans. Faraday Soc.*, 1944, **40**, 281). Since the observed difference in activation energy is only 9·4 kcals. per mole, it follows that the true rate constants in vitriol and oleum are different, and that the true activation energy in the former case (7·4 kcals. per mole) is 10·6 kcals. less than in the latter (18·0 kcals. per mole). Further, there is only one combination of sulphonating agent and proton-acceptor in accord with the kinetics, so that this activation energy difference must be ascribed (*a*) to a change in the species being sulphonated or (*b*) to a change in the physical characteristics of the medium, on passing from 98% sulphuric acid to 1% oleum.

Hypothesis (*a*) demands that RNO_2 be almost quantitatively converted into RNO_2H^+ or $RNO_2{\cdot}SO_3$ in oleum, but not in vitriol. Although $-NO_2{\cdot}SO_3$ and $-NO_2H^+$ will be more strongly electron-attracting than $-NO_2$, it is difficult to believe that the consequent increase in activation energy could be as great as 10·6 kcals. Further, as well as affecting the properties of RNO_2, such complex formation would seriously change the concentration of the sulphonating agent, sulphur trioxide; such changes are not consistent with the observed second-order kinetics.

Hypothesis (*b*) is more attractive; the transfer of a proton to the solvent may well be more difficult in oleum than in less than 98·5% sulphuric acid, where there is at least one HSO_4^- " lattice defect " for every fifteen sulphuric acid molecules. These " defects," as well as being points at which protons can very readily be accepted, will be extremely mobile; their movement involves only proton transference. It can therefore be postulated that during sulphonation in vitriol there is always a HSO_4^- " defect " near enough to any SO_3/RH collision for the proton to be transferred to the $-O^-$ group if the collision is activated. Although HSO_4^- would be involved in the critical step, its concentration would not enter into the kinetics. On the other hand, there will be very few HSO_4^- groups in 100% sulphuric acid or oleum. Here, the proton must be transferred to a neutral oxygen atom, possibly with local disruption of the lattice, and this would involve an addition to the energy of activation.

There are signs of a drop in rate constant as the water concentration falls below 1%; this may be due to the increasing scarcity of HSO_4^-, whose concentration may increasingly affect the rate as the water concentration approaches zero.

The value of $1{\cdot}6 \times 10^9$ for the non-exponential A factor in the Arrhenius equation, derived from the measurements in oleum solution, is of the correct order of magnitude for a process involving uncharged reactants such as sulphur trioxide and RH (cf. Bell, *J.*, 1943, 629). It is also relevant that it is in this type of reaction that salt effects are least important; the variations in ionic strength in the vitriol experiments are therefore unlikely to be of major importance.

The increase in apparent order of reaction when the sulphur trioxide concentration is high (>M.) may be due to thermodynamic complexities because of the large concentrations, or simply to the appearance of $HS_2O_7^-$ (a possible proton-acceptor). This would introduce an additional reaction whose rate was $k_3[RH][SO_3]\sqrt{(K_6[SO_3]^2 + K_3[SO_3])}$, the relative importance of which would be greatest (*a*) at high sulphur trioxide concentration and (*b*) at low temperature (since the activation energy would probably be less than that of the main reaction).

Interpretation of Previous Work on Sulphonation and Desulphonation.

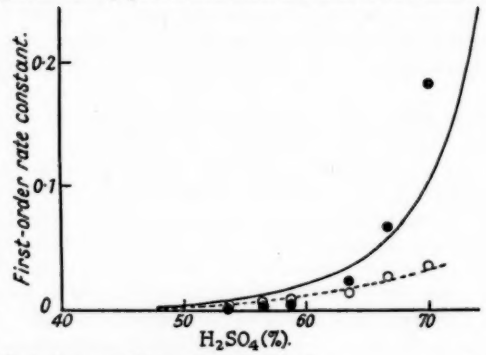
The results of Pinnow (*loc. cit.*) show that the rate of sulphonation of quinol becomes perceptible only when the sulphuric acid concentration exceeds 55%; above this concentration, the rate increases very sharply (see Fig. 4). The rate of hydrolysis of quinolsulphonic acid becomes perceptible at about the same sulphuric acid concentration, but increases with the acid concentration less sharply than the forward reaction (Fig. 4). Lantz (*Bull. Soc. chim.*, 1935, **2**, 2092) found that the rate of hydrolysis of naphthalene-α-sulphonic acid varied similarly with sulphuric acid concentration (Fig. 5). Crafts (*Ber.*, 1901, **34**, 1350; *Bull. Soc. chim.*, 1907, **1**, 917) found that the rate of hydrolysis of xylenesulphonic acids in hydrochloric acid was insignificant at low acid concentrations, but that it subsequently rose sharply (see Fig. 6).

These facts are inconsistent with the older view that the sulphonation–desulphonation equilibrium can be written as $H_2SO_4 + RH \rightleftharpoons RSO_3^- + OH_3^+$, for in this case the hydrolysis rate should be directly proportional to the acid concentration from the lowest values upward. Lantz (*Bull. Soc. chim.*, 1945, **12**, 1004) has advanced the very reasonable idea that desulphonation, which involves substitution by a proton, should be brought about best by the strongest acid in the system (sulphuric acid) and that other undissociated strong acids such as hydrochloric acid should also be effective. Such a postulate is in fact the logical counterpart of the mechanism established in this paper for sulphonation in vitriol, the complete equilibrium being $SO_3 + RH + HSO_4^- \rightleftharpoons RSO_3^- + H_2SO_4$.

In the acid concentrations under consideration (40—70%), water and not sulphuric acid is the medium, so it is likely here that the rate of the forward reaction will depend on the HSO_4^- concentration.

FIG. 4.

Pinnow's results for sulphonation of quinol and reverse reaction in moderately concentrated H_2SO_4.



Full circles : sulphonation of quinol
Open circles : hydrolysis of quinolsulphonic acid } 100°.

Full line : theoretical line for sulphonation $\left[\frac{0{\cdot}015s^3}{(w-s)^2}\right]$.

Broken line : theoretical lines for hydrolysis $\left[\frac{s^2}{30(w-s)}\right]$.

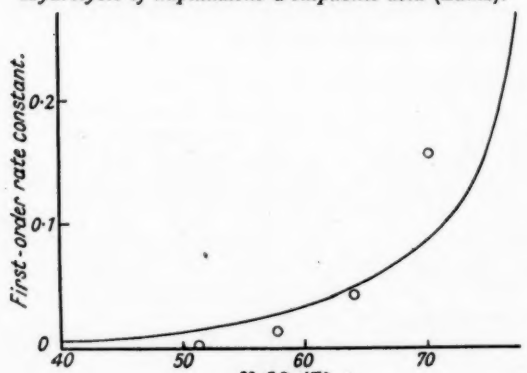
By simple and perhaps somewhat naïve mass-action considerations a solution with analytical contents w and s ($w > s$) of water and sulphuric acid respectively should contain various species in the following concentrations :

$H_2O = w - s$
$OH_3^+ = HSO_4^- = s$
$H_2SO_4 = s^2/K_7(w-s)$, K_7 being the first dissociation constant of sulphuric acid.
$SO_3 = K_1s^2/K_7^2(w-s)^2$

The rates of sulphonation and hydrolysis on this view should depend respectively on $s^3/(w-s)^2$ and $s^2/(w-s)$. Lines showing these two functions are plotted in Figs. 4 and 5, and,

FIG. 5.

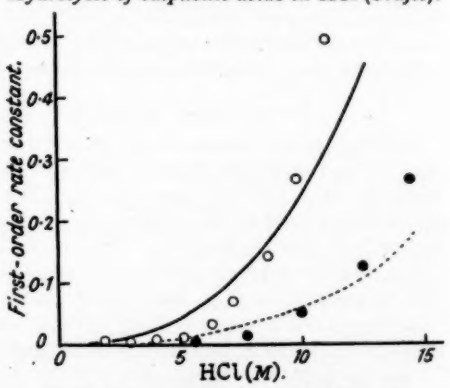
Hydrolysis of naphthalene-α-sulphonic acid (Lantz).



Line represents $s^2/10(w-s)$.

FIG. 6.

Hydrolysis of sulphonic acids in HCl *(Crafts).*



Full circles : m-*xylenesulphonic acid.*
Open circles : p-*xylenesulphonic acid.*

Broken line : $\frac{0{\cdot}02s^2}{w-s}$. *Full line :* $\frac{0{\cdot}08s^2}{w-s}$.

although agreement is not accurate (the experimental rates rise more sharply than predicted), the main features (rate negligible at low acid concentration, subsequently rising sharply) are represented. The deviations may be due to ionic interaction (the electrolyte concentrations are

between 5 and 15M.); at high acid concentrations the discrepancy may be due to the conversion of RSO_3^- into RSO_3H (which will hydrolyse at a different, unpredictable rate).

Hydrolysis rates in hydrochloric acid should, on similar grounds, depend on $s^2/(w - s)$ (s being the analytical hydrochloric acid content). Again, the main features of the reactions are shown (see Fig. 6) although there are quantitative discrepancies which could be due to the breakdown of ordinary equilibrium laws.

It can thus be claimed that a reasonable extension of the mechanism of sulphonation in 92% H_2SO_4—6% oleum provides a satisfactory and coherent working hypothesis for interpreting sulphonation and desulphonation rates in moderately concentrated acids.

The authors have greatly appreciated helpful discussions with Professor Sir Cyril Hinshelwood, F.R.S.

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400. *Deoxy-sugars. Part V. A Reinvestigation of the Glycal Method for the Synthesis of 2-Deoxy-D- and -L-ribose.*

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The glycal method for the synthesis of 2-deoxy-D- and -L-ribose has been reinvestigated and improved. The mutarotations of the deoxy-sugars in various solvents have been studied. Some new derivatives, particularly in the L-series, have been prepared and serve further to characterise this sugar.

THE chemistry of the naturally occurring 2-deoxy-D-ribose has been somewhat neglected owing to the difficulty of isolating the sugar from its natural sources and of synthesising it. Recently we have been engaged in developing methods for making the sugar available and in studying its chemical properties.

The usual preparation of 2-deoxyribose was by the well-known glycal method, whereby arabinal (prepared from arabinose by the usual standard reactions) was treated with ice-cold N-sulphuric acid. This was essentially the method of preparation employed by the early investigators of the sugar, namely Meisenheimer and Jung (*Ber.*, 1927, **60**, 1462), Gehrke and Aichner (*ibid.*, p. 918), and Felton and Freudenberg (*J. Amer. Chem. Soc.*, 1935, **57**, 1637). The best overall yield of 2-deoxy-D-ribose from D-arabinose obtained by these workers was about 5%. We considered that, in addition to developing alternative methods of synthesis of the deoxypentose, it was worth while to reinvestigate this glycal method with a view to improving the overall yield. Although we have succeeded in increasing the yield to about 10% and have developed a convenient method of purifying the sugar, there still remains the need for a general synthesis of 2-deoxy-sugars in reasonable yield.

A reliable method was first sought for the preparation of pure 1-bromo 2 : 3 : 4-triacetyl arabinose (acetobromoarabinose) in good yield. According to Felton and Freudenberg (*loc. cit.*), passing hydrogen bromide into a suspension of arabinose in acetic anhydride at 0° gives this 1-bromo-derivative rapidly and in 40% yield. Earlier, Meisenheimer and Jung (*loc. cit.*) claimed yields as high as 70%, using essentially this method. In our preliminary experiments a yield of only 30% of the 1-bromo-derivative was obtained, and consequently the acetylation and treatment of the acetylated product with hydrogen bromide were carried out in two stages. Gehrke and Aichner (*loc. cit.*) acetylated arabinose with acetic anhydride and sodium acetate, and treated the syrupy mixture of α- and β-tetra-acetyl arabinose with hydrogen bromide in glacial acetic acid; a 36% yield of 1-bromo 2 : 3 : 4-triacetyl arabinose was claimed to be afforded by this procedure. However, we have found that, when the α- and the β-form of tetra-acetyl arabinose were separated from the syrupy mixture by crystallisation of the α-isomer from aqueous alcohol, and the two forms were then separately treated with glacial acetic acid saturated with hydrogen bromide, the crystalline α-tetra-acetyl arabinose gave β-acetobromo-arabinose in good yield (84%), whereas the syrupy β-form gave only 12%. By isolating the crystalline α-tetra-acetyl arabinose and then converting this into β-acetobromoarabinose, it was possible to convert arabinose into 1-bromo 2 : 3 : 4-triacetyl arabinose in 47% yield. The crystalline β-acetobromoarabinose isolated by this method was sufficiently pure to be used without further recrystallisation. It was apparent that use of imperfectly washed crystalline material decreased the yield obtained at the next stage of the synthesis of 2-deoxyribose, so that further advantages gained by the above procedure were, first, that the quantity of syrupy

material which needed to be removed from the crystalline β-acetobromoarabinose by washing was much reduced, and secondly that the valuable arabinose could be recovered from the syrupy β-tetra-acetyl arabinose by deacetylation.

Recently, Smith and Nicholas (*Nature*, 1948, **161**, 349) reported that treatment of glucose with acetic anhydride and glacial acetic acid in the presence of perchloric acid as catalyst gave α-penta-acetyl glucose in high yield. Accordingly, since we found that α-tetra-acetyl arabinose was the most suitable for our purpose, we treated D-arabinose according to this procedure; this, however, afforded a crystalline acetylated product which differed from both α- and β-tetra-acetyl D-arabinose, and which, as yet, we have not succeeded in identifying.

β-Acetobromoarabinose was reduced to 3 : 4-diacetyl arabinal by stirring it with zinc dust in 50% acetic acid at −10°, addition of a few drops of a solution of chloroplatinic acid at intervals serving to maintain a vigorous reaction. This improvement and use of pure crystalline β-acetobromoarabinose (see above) led to a 65% yield of **3 : 4**-diacetyl arabinal. In addition to **3 : 4**-diacetyl arabinal, α-tetra-acetyl arabinose was isolated from the reaction mixture. Deacetylation of diacetyl arabinal by the method of Meisenheimer and Jung (*loc. cit.*) gave arabinal in 80% yield. 2-Deoxyribose was obtained from the arabinal by treating it with N-sulphuric acid at 0°, the best yield obtained being about 40%, for which the difficulty in crystallising 2-deoxyribose in the presence of impurities is partly responsible. It is also possible that 1-deoxyribose and 1-deoxyarabinose may result from the addition of the elements of water to the ethylenic linkage in arabinal, but the extent of this reaction is not yet known. The 2-deoxyribose was purified by recrystallisation from ethyl acetate, and gummy impurities were removed as described in the Experimental section. By this improved method, β-2-deoxy-D-ribose was prepared from D-arabinose, and β-2-deoxy-L-ribose from L-arabinose, in overall yields of about 10%.

2-Deoxyribose is insoluble in chloroform, ether, benzene, or light petroleum. It is readily soluble in water, ethyl alcohol, methyl alcohol, and pyridine, in which solvents it displays mutarotation (see Experimental section).

The velocity constant (k) for the mutarotation of 2-deoxyribose in water was calculated for both the D- and the L-form from their specific rotations. These values of k for 2-deoxyribose were 2—3 times greater than that for L-arabinose, calculated from data given by Parcus and Tollens (*Annalen*, 1890, **257**, 160). In the presence of 0·01N-hydrochloric acid or 0·01N-sodium hydroxide, 2-deoxyribose reached the equilibrium value for the specific rotation immediately on dissolution. In concentrated hydrochloric acid at room temperature, the sugar gave the equilibrium value as soon as it was dissolved, and this value surprisingly was retained for more than one hour before decomposition commenced; thereafter the specific rotation decreased slowly for several days. When 2-deoxyribose was heated with 0·5N-hydrochloric acid at 100°, the optical rotatory power of the solution progressively decreased, and lævulic acid was detected in the reaction mixture.

Since 2-deoxyribose was found to be stable for some time in concentrated hydrochloric acid at room temperature, it was possible to prepare syrupy *2-deoxy-L-ribose diethyl mercaptal* by shaking 2-deoxy-L-ribose with 2 moles of ethanethiol and concentrated hydrochloric acid. Similarly with toluene-ω-thiol, *2-deoxy-L-ribose dibenzyl mercaptal* was obtained crystalline, being readily purified by chromatography.

According to Pacsu and Green (*J. Amer. Chem. Soc.*, 1937, **59**, 1205; 1938, **60**, 2056), glycofuranosides and thioglycofuranosides are formed by controlled removal of the thio-groups from sugar mercaptals by action of an alcohol in the presence of mercuric chloride and yellow mercuric oxide. Thus, they report the preparation of crystalline α-methyl- and α-ethyl-L-arabinofuranosides. However the exclusive formation of glycofuranosides under these conditions seems doubtful, since in our hands treatment of 2-deoxy-L-ribose diethyl mercaptal with ethyl alcohol, mercuric chloride, and mercuric oxide gave an ethyl-2-deoxyriboside which, in glacial acetic acid, reduced lead tetra-acetate in amount corresponding to the presence of 10% of ethyl-2-deoxy-L-ribopyranoside in the ethyl-2-deoxyriboside isolated.

When 2-deoxy-L-ribose was heated with aniline in ethyl alcohol it afforded crystalline *2-deoxy-L-ribose anilide*. Similarly the D-isomer was prepared. These anilides have proved to be convenient derivatives for the characterisation of 2-deoxy-D- and -L-ribose.

The oxidation of 2-deoxyribose to 2-deoxyribonolactone has recently been described by Gakhokidze (*J. Gen. Chem. Russia*, 1945, **15**, 539), who however provided no polarimetric data concerning the rate of hydrolysis of the lactone, so that an investigation of this aspect seemed desirable. For converting aldoses into aldonic acids, bromine water is recognised as suitable, and the oxidation is more rapid if the hydrobromic acid produced in the reaction is removed, as

it is formed, by barium carbonate (Isbell, *J. Res. Nat. Bur. Stand.*, 1932, **8**, 615) or barium benzoate (Hudson and Isbell, *J. Amer. Chem. Soc.*, 1929, **51**, 2225). In view of the sensitivity of 2-deoxy-sugars to prolonged contact with mineral acids, comparative oxidations of 2-deoxy-L-ribose with bromine water were carried out, first using no neutralizing agent and then in the presence of calcium carbonate. The oxidation of 2-deoxy-L-ribose by bromine water alone required 4—5 days for completion, and pure 2-deoxy-L-ribonolactone was isolated in good yield (85·6%). The oxidation of 2-deoxy-L-ribose with bromine water in the presence of calcium carbonate was more vigorous and was complete in a shorter time, but the yield was lower (74·2%). A crystalline *2-deoxy-L-ribonic acid phenylhydrazide*, m. p. 145—146°, was prepared by treating the lactone with phenylhydrazine in ether (cf. Gakhokidze who reports m. p. 176—178°).

The rate of hydrolysis of 2-deoxy-L-ribonolactone and the rate of lactonization of 2-deoxy-L-ribonic acid were studied polarimetrically. Surprisingly, no change in the specific rotation of a freshly prepared solution of the lactone was observed in 8 days, and the extent of hydrolysis of the lactone is less than can be detected polarimetrically. It is noteworthy that Wolfrom *et al.* (*J. Amer. Chem. Soc.*, 1942, **64**, 1701) report similar observations on 2-deoxy-D-glucoheptonolactone and suggest that this anomalous behaviour may be due to the influence of the deoxy-group at C_2. The lactonization of 2-deoxy-L-ribonic acid required 7—8 days. The specific-rotation figures for the rate of lactonization of 2-deoxy-L-ribonic acid provided no evidence for the transient formation of a second labile lactone; if such a labile lactone is formed during the initial stages of lactonization, the polarimetric method used was not sufficiently sensitive to detect it.

Sufficient evidence has not yet been provided to decide whether the lactone is a pyrano- or a furano-lactone.

Experimental.

α-Tetra-acetyl L-Arabinose.—L-Arabinose (40 g.) was acetylated with freshly distilled acetic anhydride (200 c.c.) and powdered fused sodium acetate (20 g.) on a water-bath at 70—80° with vigorous stirring. After the initial reaction had subsided, the mixture was kept at 100° for 0·5 hour. The product was worked up in the usual way, giving a syrupy residue of α- and β-tetra-acetyl L-arabinose (80 g.) which partly crystallised after 3 days. The crystals (50 g.) were separated from the syrupy material by washing with aqueous alcohol and were identified as α-tetra-acetyl L-arabinose, m. p. 88—92°, $[\alpha]_D^{20}$ + 42·4° (*c*, 3·16 in chloroform) (cf. Gehrke and Aichner, *Ber.*, 1927, **60**, 918, who give m. p. 96—97° and $[\alpha]_D^{20}$ + 42·7° in chloroform).

Acetylation of D-Arabinose by the Perchloric Acid Method.—D-Arabinose (30·5 g.) was treated with acetic anhydride (60 c.c.), glacial acetic acid (60 c.c.), and 60% perchloric acid (0·24 c.c.) according to Smith and Nicholas (*Nature*, 1948, **161**, 349). The mixture was shaken at room temperature for 10—15 minutes, but no reaction occurred. The mixture was heated at 100° for 2 hours, the sugar then slowly dissolving. The solution, worked up as usual, gave a pale yellow syrup (40·9 g.), which gradually crystallised to a semi-solid mass. By use of benzene, the syrup was separated from the crystals, which, recrystallised from benzene, had m. p. 166—168°, $[\alpha]_D^{20}$ − 75·7° (*c*, 1·8 in chloroform) (Found: C, 47·7; H, 6·05%).

β-Acetobromo-L-arabinose.—α-Tetra-acetyl L-arabinose (96 g.) was treated with glacial acetic acid, saturated with hydrogen bromide at 0° (200 c.c.), in an ice-bath for 2 hours, according to the method of Gehrke and Aichner (*loc. cit.*). The product was poured into ice-water and extracted with chloroform. The extract was washed with sodium hydrogen carbonate solution, dried (Na_2SO_4), and freed from solvent by evaporation at 40°. The syrupy residue crystallised spontaneously, and the crystals were carefully washed free of syrupy material with ether and were stored in a vacuum over sodium hydroxide; they had m. p. 138°, $[\alpha]_D^{20}$ + 282·0° (*c*, 3·67 in chloroform) (Gehrke and Aichner, *loc. cit.*, give m. p. 139° and $[\alpha]_D^{20}$ + 283·6° in chloroform for β-acetobromo-L-arabinose).

3 : 4-Diacetyl L-Arabinal.—β-Acetobromo-L-arabinose (54 g.) was dissolved in glacial acetic acid (350 c.c.) at 30—35° and added during 10 minutes to a mechanically stirred mixture of zinc dust (108 g.) and 50% acetic acid (540 c.c.) containing a few drops of a solution of chloroplatinic acid, kept at − 10° by a freezing mixture. At intervals of 30 minutes a few drops of a solution of chloroplatinic acid were added to maintain a vigorous reaction. Sitrring was continued for 3 hours, and the mixture kept overnight at 0°. After filtration from the excess zinc dust, the filtrate was extracted with chloroform. The chloroform extracts were washed with sodium hydrogen carbonate solution and then with water and finally dried (Na_2SO_4). Removal of the solvent by evaporation at 40° afforded a syrup. Fractional distillation of this gave 3 : 4-diacetyl L-arabinal (22·0 g.) as a clear, colourless mobile liquid, b. p. 110—140°/0·01 mm., $[\alpha]_D^{19}$ − 231° (*c*, 1·6 in chloroform), and four other fractions, namely, (i) (2·7 g.) b. p. 126—150°/0·01 mm., $[\alpha]_D^{19}$ + 52·6° (*c*, 1·45 in chloroform), (ii) (4·6 g.) b. p. 150—170°/0·005 mm., $[\alpha]_D^{19}$ + 65·6° (*c*, 1·99 in chloroform), (iii) (5·8 g.) b. p. 170—190°/0·01 mm., $[\alpha]_D^{19}$ + 70·0° (*c*, 1·63 in chloroform), and (iv) (6·0 g.), b. p. 190—195°/0·01 mm., $[\alpha]_D^{19}$ + 79·8° (*c*, 2·1 in chloroform). Fractions (iii) and (iv) crystallised and were recrystallised from ethanol; both had m. p. alone or in admixture with α-tetra-acetyl L-arabinose 95—97°, $[\alpha]_D^{20}$ + 35·2° (*c*, 0·90 in chloroform) (Found: C, 48·7; H, 5·6. Calc. for $C_{13}H_{18}O_9$: C, 49·0; H, 5·6%).

L-Arabinal.—3 : 4-Diacetyl L-arabinal (41·7 g.), deacetylated by the method of Meisenheimer and Jung (*Ber.*, 1927, **60**, 1462), readily gave L-arabinal as colourless hygrosocpic needles. Recrystallisation

from benzene afforded a product (19·0 g., 79%), m. p. 79—81°, $[\alpha]_D^{20}$ − 196·0° (*c*, 3·54 in water) (Meisenheimer and Jung, *loc. cit.*, give m. p. 81—83° and $[\alpha]_D^{19}$ − 202·8° in water).

β-2-Deoxy-L-ribose.—L-Arabinal (19·0 g.) was treated with N-sulphuric acid at 0° according to Meisenheimer and Jung (*loc. cit.*). 2-Deoxy-L-ribose (8·54 g.) was obtained and was recrystallised from ethyl acetate as follows. 7·3 G. were dissolved in dry ethyl acetate (3 l.) under reflux. The solution was decanted from the insoluble material and evaporated under reduced pressure at 50° to 2·2 l. This solution was set aside at room temperature for 1—2 hours and then filtered from the brown material which had separated. After concentration of the filtrate at 50° to 840 c.c., 2-deoxy-L-ribose separated, during 3—5 days at 0°, as hard compact nodules on the sides of the vessel, and had m. p. 87—93°. Repeated recrystallisation gave β-2-deoxy-L-ribose, m. p. 92—95° (Levene and Mori, *J. Biol. Chem.*, 1929, **83**, 803, give m. p. *ca.* 80°, and Meisenheimer and Jung, *loc. cit.*, m. p. *ca.* 90°).

Optical Rotation of β-2-Deoxy-L-ribose.—The following values were recorded, values for zero time being obtained by extrapolation.

(*a*) In water (*c*, 1·14) : time (mins.) ...	0	4·25	6	8·5	21	41		
$[\alpha]_D^{16\cdot5}$	+80°	+72·5°	+71°	+66°	+59°	+59°		
(*b*) In methanol (*c*, 0·90) : time (mins.)	0	3·5	6·5	9·5	12·5	27·5	81·5	136·5
$[\alpha]_D^{20}$	+105°	+87°	+76°	+71°	+67°	+58°	+49°	+49°
(*c*) In ethanol (*c*, 1·07) : time (mins.)...	0	9	25	75	135	20 (hr.)		
$[\alpha]_D^{18}$	+89°	+78°	+71°	+47°	+37°	+37°		
(*d*) In pyridine (*c*, 0·75) : time (mins.)	0	22	72	137	217	3 (days)		
$[\alpha]_D^{18\cdot5}$	+95°	+85°	+69°	+58°	+53°	+45°		

Levene and Mori (*loc. cit.*) quote $[\alpha]_D^{25}$ +92° (initial) ⟶ +40·5° (equilibrium) in pyridine.

β-2-Deoxy-D-ribose.—β-2-Deoxy-D-ribose was prepared from β-D-arabinose by the method used for β-2-deoxy-L-ribose. After one recrystallisation from ethyl acetate, β-2-deoxy-D-ribose had m. p. 96—98° (Gakhokidze, *J. Gen. Chem. Russia*, 1945, **15**, 539, gives m. p. 91°) (Found : C, 44·7; H, 7·4. Calc. for $C_5H_{10}O_4$: C, 44·8; H, 7·5%).

Optical Rotational of β-2-Deoxy-D-ribose.—The following values were recorded, values for zero time being obtained by extrapolation.

(*a*) In water (*c*, 1·65) :									
time (mins.).....	0	2·5	3·5	5	7	10·5	14·5	23·5	61·5
$[\alpha]_D^{17}$.....	−91°	−82°	−81°	−75°	−71°	−63°	−59°	−58°	−58°
(*b*) In methanol (*c*, 5·8) :									
time (mins.).....	0	4	11·5	19·5	33	100	180	285	24 hr.
$[\alpha]_D^{20\cdot5}$	−96·9°	−93°	−87°	−83°	−76°	−57°	−50°	−46°	−46°
(*c*) In ethanol (*c*, 2·1) :									
time (mins.).....	0	15	30	73	115	215	265	295	
$[\alpha]_D^{20}$.....	−99°	−81°	−71°	−57°	−50°	−40°	−36°	−36°	
(*d*) In pyridine (*c*, 3·0) :									
time (mins.).....	0	4	13	71	141	242	19·5 hr.	23 hr.	25 hr.	43·5 hr.
$[\alpha]_D^{20}$.....	−106°	−104°	−102°	−93°	−83°	−76°	−47°	−45°	−42°	−41°

Treatment of 2-Deoxyribose with Acid.—(*a*) When 2-deoxy-L-ribose (0·048 g.) was dissolved in concentrated hydrochloric acid (5 c.c.), polarimetric observations were as follows : $[\alpha]_D$ + 35° (5 mins.), + 35° (82 mins.), + 17° (15 hrs.), and + 12° (26 hrs.). No coloration of the solution was observed.

(*b*) When 2-deoxy-L-ribose (0·034 g.) was heated with 0·5N-hydrochloric acid (6 c.c.) at 100°, polarimetric observations were as follows : $[\alpha]_D$ + 50° (initially), + 39° (10 mins.), + 21° (25 mins.), and + 14° (70 mins.). The solution became progressively more coloured, and after 70 minutes no further readings could be taken; it gave a positive iodoform test for lævulic acid.

2-Deoxy-L-ribose Diethyl Mercaptal.—2-Deoxy-L-ribose (1·2 g.) was dissolved in concentrated hydrochloric acid (2 c.c.) at 0° and ethanethiol (1·5 c.c., 36% excess) was added. After 5 minutes' shaking at 0°, the mixture was diluted with water (20 c.c.) and extracted several times with chloroform. The combined chloroform extracts (100 c.c.) were washed with, successively, water, sodium hydrogen carbonate solution, and water. The chloroform extract was dried (Na_2SO_4), and the solvent removed by evaporation *in vacuo* at 40°. The residual *2-deoxy-L-ribose diethyl mercaptal* (1·39 g.) was distilled, to give a colourless viscous syrup (0·835 g.), b. p. 170—175°/0·06 mm., n_D^{20} 1·5385, $[\alpha]_D^{20}$ + 8·8° (*c*, 0·96 in ethyl alcohol) (Found : C, 45·6; H, 8·5. $C_9H_{20}O_3S_2$ requires C, 44·9; H, 8·3%).

2-Deoxy-L-ribose Dibenzyl Mercaptal.—2-Deoxy-L-ribose (3·75 g.) was mixed with toluene-ω-thiol (7·0 c.c., 7% excess), and the mixture cooled to 0°. Concentrated hydrochloric acid (7·0 c.c.) was added and the mixture shaken for 5—10 minutes. After chloroform (25 c.c.) had been added, the mixture was poured into water, and the chloroform layer removed. The aqueous solution was further extracted with chloroform (50 c.c.). The combined chloroform extracts were washed with, successively, water, sodium hydrogen carbonate solution, and water, and dried (Na_2SO_4), and the solvent removed by evaporation *in vacuo* at 40°. Crystallisation of the residual syrup (9·1 g.) gave some crude solid material (5·0 g.). Recrystallisation from ether–light petroleum (2 : 1 by volume) gave *2-deoxy-L-ribose dibenzyl mercaptal* (2·5 g.), m. p. 66—70°, unchanged by further recrystallisation, $[\alpha]_D^{20}$ − 12·0° (*c*, 1·6 in chloroform) (Found : C, 61·3; H, 6·7. $C_{19}H_{24}O_3S_2$ requires C, 62·6; H, 6·7%).

Further quantities of 2-deoxy-L-ribose dibenzyl mercaptal were obtained by chromatography of the combined syrupy residues which were placed on an alumina column (30 × 1 cm.) wetted with benzene–light petroleum (1 : 1 by volume). Elution of the column with this solvent mixture first removed

toluene-ω-thiol with some 2-deoxy-L-ribose dibenzyl mercaptal. The remaining mercaptal (3 g.) was removed completely after successive elution with benzene, chloroform, and ethyl alcohol; crystallisation of this material after removal of the solvents gave 2-deoxy-L-ribose dibenzyl mercaptal (2·35 g.), m. p. 62—68°, free from toluene-ω-thiol.

Ethyl-2-deoxy-L-riboside.—2-Deoxy-L-ribose diethyl mercaptal (0·835 g.) was dissolved in ethanol (12 c.c.), and to the solution mercuric oxide (1·87 g.) and mercuric chloride (1·9 g.) were added. The mixture was shaken at room temperature for 2 hours and then filtered. Subsequent operations were carried out according to Pacsu (*loc. cit.*). The material finally obtained was a syrup (0·5 g.) which was distilled, giving a colourless viscous syrup (0·246 g.), b. p. 110—120°/0·1 mm. (approx.), $[\alpha]_D^{21}$ − 26·5° (*c*, 4·5 in ethanol), which did not crystallise (Found: OEt 26·1. $C_7H_{14}O_4$ requires OEt, 27·8%). The *compound* gave a negative test for sulphur and a negative Fehling's test. Treatment with lead tetra-acetate in glacial acetic acid resulted in the uptake of 0·1 mol. corresponding to the presence of 10% of ethyl-2-deoxyribopyranoside in the syrup.

2-Deoxy-L-ribose Anilide.—2-Deoxy-L-ribose (0·146 g.) was heated under reflux for 4 hours with the theoretical quantity of freshly distilled aniline (0·112 g.) in ethyl alcohol (3·4 c.c.). The solution was allowed to cool, and *2-deoxy-L-ribose anilide* (0·137 g.) crystallised. Recrystallisation from ethyl alcohol gave colourless needles, m. p. 169·5—170·5° (Found: C, 63·3; H, 7·3; N, 6·3. $C_{11}H_{15}O_3N$ requires C, 63·1; H, 7·2; N, 6·7%).

2-Deoxy-D-ribose Anilide.—2-Deoxy-D-ribose (0·045 g.) was heated under reflux for 4 hours with the theoretical quantity of freshly distilled aniline (0·0347 g.) in ethyl alcohol (2·78 c.c.). On cooling, crystals of 2-deoxy-D-ribose anilide were deposited, having m. p. 168°, $[\alpha]_D^{20}$ + 19·5° (*c*, 0·21 in ethyl alcohol). The material was soluble in methyl alcohol, sparingly soluble in ethyl alcohol, and insoluble in water or chloroform. Treatment of the anilide with lead tetra-acetate in glacial acetic acid resulted in its complete decomposition.

2-Deoxy-L-ribonolactone.—2-Deoxy-L-ribose (0·5 g.) was dissolved in water (3 c.c.). Calcium carbonate (0·75 g.) and bromine (1·0 c.c.) were added to the solution. The reaction mixture was shaken and set aside for 2 days. The solution, which then did not reduce Fehling's solution, was aërated to remove excess of bromine and filtered from the excess of calcium carbonate. Oxalic acid (1·0 g.) was dissolved in the filtrate, and an excess of silver carbonate was immediately added. The syrupy mixture was isolated in the usual way. The residual syrup was lactonized by being heated at 70°/12 mm., and 2-deoxy-L-ribonolactone (0·365 g.) was obtained, having n_D^{20} 1·4834 (Found: equiv., 131. Calc. for $C_5H_8O_4$: equiv., 132).

(ii) 2-Deoxy-L-ribose (0·5 g.) was dissolved in water (3 c.c.), and bromine (1 c.c.) added. The mixture was shaken and set aside for 5 days. The product, which did not reduce Fehling's solution, was isolated as usual as a syrup (Found: C, 39·6; H, 5·8. Calc. for $C_5H_{10}O_5$: C, 40·0; H, 6·7%). This was lactonized by heating it for 2 hours at 70°/12 mm., to yield 2-deoxy-L-ribonolactone (Found: equiv., 125; C, 45·6; H, 6·4. Calc. for $C_5H_8O_4$: C, 45·6; H, 6·1%), n_D^{20} 1·4821, $[\alpha]_D^{20}$ − 13·8° (initial) ⟶ − 14·5° (in 8·29 days) (in water) (Gakhokidze, *J. Gen. Chem. Russia*, 1940, **10**, 497, gives m. p. 153—155° and $[\alpha]_D^{19}$ 2·1°). The lactone (0·00967 g.) was dissolved in 0·6N-sodium hydroxide (0·150 c.c.), and the solution kept at 40° for 6 hours. After a further hour at room temperature, the solution was exactly neutralised with hydrochloric acid (0·152 c.c.) and then had $[\alpha]_D^{20}$ + 8·16° (initial), becoming − 11·2° in 8·1 days. For 2-deoxy-L-ribonic acid Gehrke and Aichner (*Ber.*, 1927, **60**, 918) give $[\alpha]_D$ + 8·5° ⟶ −10·7°, and Levene, Mikeska, and Mori (*J. Biol. Chem.*, 1930, **85**, 785) reported $[\alpha]_D$ + 8·5° ⟶ −12·2°.

2-Deoxy-L-ribonic Acid Phenylhydrazide.—2-Deoxy-L-ribonolactone (0·046 g.) was mixed with the exact equivalent of phenylhydrazine in ether (0·721 c.c. of a solution containing 0·0209 g. in 4·0 c.c. of solution). The ether was removed by evaporation under reduced pressure at 30°, and the resultant product recrystallised from acetone, giving *2-deoxy-L-ribonic acid phenylhydrazide* (7 mg.) as pale yellow crystals, m. p. 145—146° (after four recrystallisations) (Found: C, 54·9; H, 6·9. $C_{11}H_{16}O_4N_2$ requires C, 55·0; H, 6·7%). Gakhokidze (*J. Gen. Chem. Russia*, 1945, **15**, 539) reports m. p. 176—178° for the compound isolated from this reaction.

The analyses were carried out by Dr. W. T. Chambers to whom our thanks are due. One of us (W. G. O.) thanks the Board of the British Rubber Producers' Research Association for financial assistance and another (E. G. T.) acknowledges with gratitude the award of a Beit Fellowship for Medical Research. We thank also the British Empire Cancer Campaign (Birmingham branch) for financial assistance.

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401. *The Alkylation of Nitrourethane and of* N-*Nitrotoluene*-p-*sulphonamide.*

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Nitrourethane can be alkylated, by means of diazohydrocarbons, to yield, eventually, primary nitroamines which are otherwise inaccessible. Other reactions investigated were less satisfactory, though *N*-nitro-*N*-alkyltoluene-*p*-sulphonamides can be hydrolysed in good yield to the nitroamine. Some *S*-benzylthiuronium salts of nitroamines are reported.

IN the course of a study of the stability of primary nitroamines towards alkali it appeared desirable to prepare some examples without using nitric acid at a late stage of the synthesis. This can be achieved if the intermediate secondary nitroamines are prepared by alkylation instead of nitration, and some of the compounds reported are probably inaccessible by standard methods.

Nitrourethane (I) is converted by the appropriately substituted diazomethane into secondary nitroamides, which, without isolation, are ammonolysed to yield the ammonium salts of benzyl-*benzhydryl-*, 4 : 4′-*dimethylbenzhydryl-*, and 4 : 4′-*dibromobenzhydryl-nitroamine* (II; R = Ph, R′ = H) and (II; R = R′ = Ph, C_6H_4Me, or C_6H_4Br).

$$\underset{\text{(I.)}}{EtO_2C{\cdot}NH{\cdot}NO_2} + N_2CRR' \xrightarrow{-N_2} EtO_2C{\cdot}N(NO_2){\cdot}CHRR' \xrightarrow{+2NH_3} CHRR'{\cdot}N{\cdot}NO_2 + NH_2{\cdot}CO_2Et$$

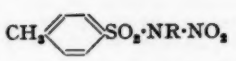
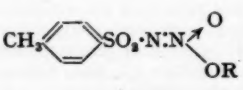
$$\text{(II.)}\quad \widetilde{NH_4}$$

The utility of the process depends on the availability of the required diazohydrocarbon, and, as these were prepared from the ketone (or aldehyde) through the hydrazone, the complete synthesis converts >C=O into $-CH{\cdot}NH{\cdot}NO_2$. The yield, from equimolecular proportions of nitrourethane and diazohydrocarbon, is 40—70%. In contrast with early work using diazomethane (Heinke, *Ber.*, 1898, **31**, 1395) there is some evidence of the formation of *O*-alkylnitroamides, as well as the required *N*-alkyl compounds.

Although Staudinger and Kupfer (*Ber.*, 1911, **44**, 2211) failed to prepare a diazo-compound from Michler's ketone, we obtained, by the use of mercuric oxide and a potassium hydroxide catalyst, a highly coloured oxidation product of the hydrazone. This may be crude 4 : 4′-bisdimethylaminodiphenyldiazomethane. We were unable to prepare the corresponding benzhydrylnitroamine from this material.

Alternative methods of alkylation have been investigated, but appear to be less satisfactory. Thiele and Lachman (*Annalen*, 1895, **288**, 291) converted the silver salt of nitrourethane into *N*-nitro-*N*-methylurethane by the action of methyl iodide at room temperature. This has been confirmed, but, in the case of benzyl halides, warming in ligroin was necessary to hasten the reaction. Attempts to alkylate with triphenylmethyl chloride were unsuccessful.

N-Nitro-*N*-alkylsulphonamides have previously been prepared by nitration (Romburgh, *Rec. Trav. chim.*, 1884, **3**, 14; Ssolonina, *Zentr.*, 1899, II, 867) and, in one instance (*N*-nitro-*N*-methylbenzenesulphonamide; Hinsberg, *Ber.*, 1892, **25**, 1095), by alkylation, but their utility as intermediates in the synthesis of primary nitroamines had not been examined. The silver salt of *N*-nitrotoluene-*p*-sulphonamide has been converted by methyl iodide, in ether at room temperature or in hot dioxan, into the N-*methyl* derivative (III; R = Me) in 45% yield. Treatment with benzyl chloride in dioxan at 100°, or in ether at room temperature, gives small yields of the N- and, presumably, the O-*benzyl* derivative (III and IV; R = CH_2Ph), respectively.

(III.)  (IV.) 

Romburgh (*loc. cit.*) reported that *N*-nitro-*N*-methylbenzenesulphonamide was slowly decomposed by boiling with aqueous potassium carbonate, but the decomposition products do not appear to have been isolated. We found that, in contrast with the *N*-nitro-*N*-alkylurethanes, the *N*-nitro-*N*-alkyltoluene-*p*-sulphonamides did not react with ammonia in ether. They were, however, decomposed by hot aqueous sodium hydroxide with elimination of the toluene-*p*-sulphonyl group to produce, in the cases investigated, methyl- and benzylnitroamines, respectively, in 90% yields. Their structure was proved by this hydrolysis, and by the ready synthesis of the *N*-methyl compound by direct nitration of *N*-methyl toluene-*p*-sulphonamide.

Derivatives of benzyl alcohol and of *N*-nitrotoluene-*p*-suphonamide could be prepared from the decomposition products which were obtained when the presumed *O*-benzyl derivative (IV; R = CH_2Ph) was heated with aqueous sodium hydroxide.

Small quantities of low-melting nitroamines may be conveniently identified as the *S*-benzylthiuronium salts. The properties of a number of these salts are tabulated on p. 1886.

Experimental.

N-Alkylation of Nitrourethane with Diazohydrocarbons.—Since the subsequent reaction with nitrourethane appeared to take place more smoothly, and with a slightly better yield, in benzene than in ether, the diphenyldiazomethanes (Staudinger and Goldstein, *Ber.*, 1916, **49**, 1923: Staudinger, Anthes, and Pfenninger, *Ber.*, 1916, **49**, 1932) were prepared in benzene solution. Phenyldiazomethane was prepared as by Staudinger (*ibid.*, p. 1906), with the addition of a pellet of solid potassium hydroxide

as a catalyst (compare *Org. Synth.*, Coll. Vol. II, p. 496). The available diazohydrocarbon was estimated by treatment of an aliquot with excess of benzoic acid. To measure this excess conveniently it was found advisable to transfer the unused benzoic acid to the aqueous layer by shaking with 0·1N-sodium hydroxide, and to titrate the excess of alkali with hydrochloric acid, using phenolphthalein as indicator.

The benzene solution (strength between 0·5M. and 0·1M.) of the diazohydrocarbon was added to an equimolecular quantity of nitrourethane dissolved in the minimum volume of ether. After being kept overnight, the solution was warmed to 40° for ½ hour, cooled, and treated with gaseous ammonia. The precipitated ammonium salt of the nitroamine was collected, washed with benzene, dissolved in water, and decomposed with dilute hydrochloric acid, to yield the insoluble nitroamine with elimination of any residual water-soluble nitrourethane. The following were thus obtained: benzylnitroamine (Thiele, *Annalen*, 1910, **376**, 256) (42%), m. p. 35—37°; *benzhydrylnitroamine* (55%), crystallisable from ether–ligroin to give prisms, m. p. 86° (Found: C, 68·6; H, 5·4; N, 12·6; equiv., 226. $C_{13}H_{12}O_2N_2$ requires C, 68·4; H, 5·3; N, 12·6%; equiv., 228); and 4 : 4′-*dibromobenzhydrylnitroamine* (59%), crystallisable from *cyclo*hexane to give felted needles, m. p. 118—119° (Found: C, 40·5; H, 2·8; N, 6·6; equiv., 390. $C_{13}H_{10}O_2N_2Br_2$ requires C, 40·4; H, 2·6; N, 7·3%; equiv., 386). Precipitation of the ammonium salt of the nitroamine did not always occur rapidly, and in the case of 4 : 4′-*dimethylbenzhydrylnitroamine* decomposition with 2·5 molecular proportions of *iso*propylamine was preferable to the use of ammonia; after the mixture had been kept at room temperature overnight, the *iso*propylamine salt was collected and decomposed by shaking a suspension of it in dilute hydrochloric acid with ether. The nitroamine was reprecipitated as the ammonium salt, and worked up as previously described. Yield, 67%; fine needles, m. p. 91—92° (from *cyclo*hexane) (Found: C, 70·3; H, 6·0; N, 11·1; equiv., 255. $C_{15}H_{14}O_2N_2$ requires C, 70·3; H, 6·3; N, 10·9%; equiv., 256).

Closer Investigation of the Reaction between Nitrourethane and Diphenyldiazomethane. Evidence for Partial O-*Alkylation.*—Preliminary experiments in ethereal solution showed that a molecular ratio of 3 : 2 in favour of the diazohydrocarbon gave a yield (nitrourethane to nitroamine) of about 45%, and that ratios of 1·2 : 1 or 2·4 : 1 in favour of nitrourethane gave yields (diazo-compound to nitroamine) of about 40%. It therefore appeared likely that interaction was complete, but occurred only partly in the desired direction.

In two further experiments in benzene, nitrourethane was treated with a slight excess (1·01 and 1·02 mols.) of diphenyldiazomethane. The ammonium salt obtained was converted into the nitroamine in 88 and 90% yield. These figures were not exceeded in the earlier experiments using a large excess of diazohydrocarbon. The crude salt thus contained little, if any, ammonium nitrourethane, and therefore the nitrourethane which did not undergo *N*-alkylation did not remain free. The mother-liquors, after precipitation of the ammonium salt, were evaporated *in vacuo*, and, after the residual oil had been shaken with water, crude benzhydrol was isolated in yields corresponding to the nitrourethane lost (1·0 and 1·1 mols. per mol. of nitrourethane not suffering *N*-alkylation).

Additional proof that the whole of the nitrourethane enters into the reaction (and disproof of the logically possible, but chemically unlikely, proposition that the base decomposed *N*-nitro-*N*-benzhydrylurethane with only partial production of the nitroamine) was obtained by the use of *cyclo*hexylamine in place of ammonia. From equimolecular proportions of nitrourethane and diphenyldiazomethane the yield of *cyclo*hexylamine salt (convertible in 93% yield into nitroamine) was 43%, and the carbethoxyl group was recovered almost quantitatively as N-*cyclohexylurethane* (94%), m. p. 48—51° (identified by mixed m. p. with a pure specimen, m. p. 56°), by evaporation of the filtrate from the *cyclo*hexylamine nitroamine salt and distillation *in vacuo*. Benzhydrol (m. p. 55—62°, identified by mixed m. p. with authentic material) was obtained in 34% yield as the second fraction of the distillate.

These results could be explained in terms of *O*-alkylation, succeeded by the decomposition: $CHPh_2{\cdot}O{\cdot}N(O){:}N{\cdot}CO_2Et + C_6H_{11}{\cdot}NH_2 \longrightarrow CHPh_2{\cdot}OH + N_2O + C_6H_{11}{\cdot}NH{\cdot}CO_2Et$. An attempt was made to demonstrate the evolution of gas by treatment with *cyclo*hexylamine in a Torricellian vacuum, using chlorobenzene as a solvent. Whilst qualitative evidence of gas evolution (by comparison with a control) was obtained, the yield, even after heating with steam, was only about 40% of that anticipated, and thus we cannot consider that a satisfactory solution of the question has yet been achieved. Furthermore, when the mother-liquor from the precipitation of ammonium benzylnitroamine was evaporated and distilled, we obtained, in addition to urethane, a considerable quantity of benzyl allophanate, m. p. 185°, identified by analyses (Found: C, 55·5; H, 5·0; N, 14·7. Calc. for $C_9H_{10}O_3N_2$: C, 55·7; H, 5·2; N, 14·4%) and by mixed m. p. with authentic material; no allophanate was isolated when synthetic mixtures of urethane and benzyl alcohol were heated or distilled.

Authentic benzyl allophanate, m. p. 185° (Found: C, 55·7; H, 5·1; N, 14·5%), was prepared by the method of Béhal (*Bull. Soc. chim.*, 1919, [iv], **25**, 475), using a current of nitrogen, in place of carbon dioxide, to carry the cyanic acid vapour. Béhal (*loc. cit.*, p. 479) reported m. p. 121° but no analyses; Traube (*Ber.*, 1889, **22**, 1573) gave m. p. 183°, even though his nitrogen analysis was poor, the calculated figure given being erroneous.

Attempted Preparation of 4 : 4′-*Bisdimethylaminodiphenyldiazomethane.*—The hydrazone (2·8 g.) (Wieland and Roseeu, *Annalen*, 1911, **381**, 232) from Michler's ketone was shaken for 15 minutes with mercuric oxide (2·4 g.) in ligroin (30 ml.; b. p. 60—80°), with the addition of alcoholic potassium hydroxide (1 ml.; 1·5N.) as catalyst. The resultant paste was dissolved in hot ligroin, filtered, and allowed to cool. Dark blue needles, m. p. 97° (decomp.), separated and were analysed on the same day (Found: C, 73·7, 73·9, 74·1; H, 7·2, 7·0, 7·1; N, 18·4, 18·0. The *diazo*-compound $C_{17}H_{20}N_4$ requires C, 72·8; H, 7·2; N, 20·0%).

Benzylnitroamine by Alkylation of Silver Nitrourethane.—Stirring silver nitrourethane (0·48 g.) (Thiele and Lachman, *Annalen*, 1895, **288**, 290) with benzyl iodide (0·2 g.) in ether (8 ml.) in a Thiele-type ball-mill (*Annalen*, 1895, **288**, 291) for 5 days yielded only a trace of nitroamine on ammonolysis.

Silver nitrourethane (0·48 g.) was boiled under reflux with benzyl chloride (0·5 ml.) in ligroin (5 ml.; b. p. 60—80°) for 8 hours, severe " bumping " being controlled by the addition of a little sand. After filtration, the solution of benzylnitrourethane was worked up by evaporation, dissolution in ether, ammonolysis, collection of the precipitate, and acidification to yield benzylnitroamine (70 mg.,

identified by conversion into the *S*-benzylthiuronium salt). A yield of 90 mg. was obtained by the use of benzyl iodide in place of the chloride.

Silver N-*Nitrotoluene*-p-*sulphonamide*.—Toluene-*p*-sulphonamide (10 g.) was dissolved in nitric acid (50 ml.; 70% w/w) at −10°, and 98% nitric acid (50 ml.) added gradually with stirring and cooling to 0°. A few minutes later, when a sample was found to be completely soluble in a large volume of water, the main bulk was poured on ice (*ca.* 250 g.). The nitro-amide was collected, and, without draining on the filter, washed with a little ice water; the damp precipitate was dissolved in 2N-ammonium hydroxide to give a neutral solution and warmed, and silver nitrate (10 g. in a little water) added. The silver salt (14 g.), m. p. 219°, (Matthews, *J. Phys. Chem.*, 1920, **24**, 108), separated on cooling (Found: Ag, 33·6. Calc. for $C_7H_7O_4N_2SAg$: Ag, 33·4%).

N-*Methyltoluene*-p-*sulphonamide* (III; R = Me).—(a) *By nitration*. *N*-Methyltoluene-*p*-sulphonamide (23 g.) was added portionwise at −5° to nitric acid (130 ml.; 70% w/w). After dissolution had occurred, 98% nitric acid (130 ml.) was added gradually at 0°, and stirring continued for 10 minutes at the same temperature. The N-*Methyltoluene*-p-*sulphonamide* was precipitated by pouring into ice–water, collected, and crystallised from methylated spirit to yield stout needles (21 g.), m. p. 57° (Found: C, 41·7; H, 4·1; N, 12·4. $C_8H_{10}O_4N_2S$ requires C, 41·8; H, 4·4; N, 12·2%).

(b) *By alkylation*. Silver *N*-nitrotoluene-*p*-sulphonamide (2 g.) was stirred in a ball-mill (Thiele, *loc. cit.*) for 15 hours at room temperature with methyl iodide (1 g.) and ether (8 ml.). The filtrate from silver iodide was evaporated, and the residue crystallised from methylated spirit to yield 0·65 g. of material identified by m. p. and mixed m. p. with that obtained by nitration (Found: C, 42·1; H, 4·3; N, 11·9%). A similar yield was obtained by heating the silver salt (1·6 g.) under reflux for 2 hours with methyl iodide (0·7 g.) in dioxan (30 ml.).

N-*Nitro*-N-*benzyltoluene*-p-*sulphonamide* (III; R = CH_2Ph).—Silver *N*-nitrotoluene-*p*-sulphonamide (1·6 g.) was heated under reflux for 4 hours with benzyl chloride (0·7 g.) in dioxan (30 ml.). The filtrate from silver chloride was evaporated *in vacuo*, taken up in ether, refiltered from dioxan-soluble material and re-evaporated *in vacuo* with warming to remove traces of benzyl chloride. The residue was crystallised from methylated spirit to yield N-*nitro*-N-*benzyltoluene*-p-*sulphonamide* (0·25 g.) as needles, m. p. 79° (Found: C, 54·7; H, 3·9; N, 9·3. $C_{14}H_{14}O_4N_2S$ requires C, 54·9; H, 4·6; N, 9·2%).

N-*Nitro*-O-*benzyltoluene*-p-*sulphonamide* (IV; R = CH_2Ph).—Silver *N*-nitrotoluene-*p*-sulphonamide (2·0 g.) was stirred in a ball-mill (Thiele, *loc. cit.*) for 1 week with benzyl chloride (0·7 ml.) and ether (8 ml.). The filtrate from silver chloride was evaporated, and the residue crystallised from *cyclo*hexane to yield the presumed N-*nitro*-O-*benzyltoluene*-p-*sulphonamide* (0·7 g.), m. p. 66—68°, depressed to 50—60° by admixture with the *N*-benzylamide, m. p. 79°) (Found: C, 54·9; H, 4·8; N, 9·4. $C_{14}H_{14}O_4N_2S$ requires C, 54·9; H, 4·6; N, 9·2%). The *cyclo*hexane mother-liquor yielded the *N*-benzyl compound (0·2 g.), m. p. 79°, on evaporation and crystallisation from methylated spirit. In contrast to the stable *N*-benzyl compound, the *O*-benzylamide showed considerable decomposition after storage for a few weeks. Passage of ammonia through an ethereal solution of the partly decomposed material gave a precipitate identified as the ammonium salt of *N*-nitrotoluene-*p*-sulphonamide by conversion into the *S*-benzylthiuronium salt.

Decomposition of the N-*Nitro*-N-*alkyltoluene*-p-*sulphonamides*.—No salt precipitation occurred when ammonia was passed into ethereal solutions of the *N*-methyl, the *N*-benzyl, or the *O*-benzyl compound.

N-Nitro-*N*-methyltoluene-p-sulphonamide (2·3 g.) was heated under reflux with N-sodium hydroxide (20 ml.) until dissolution was complete (1 hour) and no ether-soluble material remained. The solution was acidified, and methylnitroamine (0·68 g., m. p. 32—36°) isolated by continuous ether extraction and evaporation.

N-Nitro-*N*-benzyltoluene-*p*-sulphonamide (0·31 g.) was heated under reflux with 0·1N-sodium hydroxide (20 ml.) until complete solution was obtained (3½ hours). Nitrobenzylamine (0·14 g.), m. p. 32—34°, was then isolated by acidification, ether extraction, and evaporation.

N-Nitro-*O*-benzyltoluene-*p*-sulphonamide (0·31 g.) was heated under reflux with 0·1N-sodium hydroxide (20 ml.) for 2 hours. The alkaline solution was extracted with ether, and this yielded a liquid (0·11 g.) on evaporation; this crude liquid was converted into benzyl 3 : 5-dinitrobenzoate (0·13 g.), m. p. 110—112°, identified by mixed m. p. with an authentic specimen. The alkaline solution was acidified and extracted with ether: on evaporation there was obtained a gum (0·09 g.) which yielded the *S*-benzylthiuronium salt of *N*-nitrotoluene-*p*-sulphonamide, m. p. 128—134° (identified by mixed m. p. with authentic material), on neutralisation and treatment with *S*-benzylthiuronium hydrochloride.

Preparation of S-*Benzylthiuronium Salts*.—(*a*) The nitroamine or nitroamide (0·001 mol.) was neutralised with 0·2N-sodium hydroxide (5 ml.), just re-acidified to phenolphthalein with 0·1N-hydrochloric acid, and aqueous *S*-benzylthiuronium hydrochloride (2·2 ml.; 0·5 N.) added. After cooling in ice, the salt

S-*Benzylthiuronium Salts of Nitroamines and Nitroamides.*

Salt of	Method of prep.	Yield, %, as pptd.	M. p. of pure salt.	Found (%). C.	H.	N.	Formula.	Required (%). C.	H.	N.
Methylnitroamine	*a*	75	117°	44·9	5·6	23·7	$C_9H_{14}O_2N_4S$	44·6	5·8	23·1
Ethylenebisnitroamine	*b*	28	125—129 (decomp.)	44·9	5·3	23·1	$C_{18}H_{26}O_4N_8S_2$	44·8	5·4	23·2
Benzylnitroamine	*a*	84	127	57·0	5·5	18·0	$C_{15}H_{18}O_2N_4S$	56·6	5·7	17·6
Benzhydrylnitroamine	*a*	95	144	64·3	5·4	14·4	$C_{21}H_{22}O_2N_4S$	63·9	5·6	14·2
4 : 4′-*Dibromobenzhydryl-nitroamine*	*a*	96	165 (decomp.)	46·2	3·6	10·0	$C_{21}H_{20}O_2N_4SBr_2$	45·8	3·6	10·1
Nitrourethane	*b*	68	154 (decomp.)	43·9	5·3	18·8	$C_{11}H_{16}O_4N_4S$	44·0	5·4	18·7
N-*Nitrotoluene*-p-*sulphonamide*	*a*	95	136	47·7	4·8	15·1	$C_{15}H_{18}O_4N_4S_2$	47·1	4·7	14·7

was collected and recrystallised from 50% aqueous alcohol. In the case of methylnitroamine, 1 ml. of N-sodium hydroxide was used in place of 5 ml. of 0·2N.

(*b*) The nitroamine or nitroamide (0·006 mol.) was dissolved in N-sodium hydroxide (6·5 ml.), neutralised with 0·1N-hydrochloric acid, and added to a hot solution of *S*-benzylthiuronium hydrochloride (1 g. in 7 ml. of alcohol). After cooling in ice, the salt was collected and recrystallised from alcohol.

The *S*-benzylthiuronium salts whose properties are tabulated exhibited sharp melting points, though these were in some cases dependent on the rate of heating. Identification by means of mixed melting points was satisfactory. For satisfactory analyses it was necessary to mix the salts with copper oxide before combustion.

N-cyclo*Hexylurethane*.—Ethyl chloroformate (30 ml.) was added in 10 minutes to *cyclo*hexylamine (35 ml.) and 2N-sodium hydroxide (160 ml.) with stirring and cooling to maintain the temperature at about 50°. After a further 10-minutes' stirring, the mixture was cooled, and ether added. The ethereal solution was washed with sodium hydroxide, hydrochloric acid, and water; after drying, N-cyclo*hexylurethane* was isolated by evaporation and distillation *in vacuo*; yield, 46 g.; b. p. 123°/11 mm.; m. p. 56° (Found: C, 62·9; H, 9·9. $C_9H_{17}O_2N$ requires C, 63·1; H, 10·0%).

The (semi-micro)analyses were performed by Mr. Rex Oldale, to whom we are indebted for observations on the combustion of the *S*-benzylthiuronium salts.

During a part of this work one of us (M. I. G.) has been in receipt of a grant from the Ministry of Supply, and we thank the Chief Scientist, Ministry of Supply, for permission to publish it.

THE UNIVERSITY, SHEFFIELD, 10. [*Received, February 15th*, 1949.]

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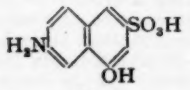
402. *Aminohydroxynaphthoic Acids. Part I. Synthesis of 6-Amino-4-hydroxy-2-naphthoic Acid ("Carboxy γ-Acid").*

By W. F. BEECH and N. LEGG.

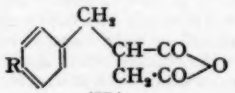
Nitration of 4-keto-1 : 2 : 3 : 4-tetrahydro-2-naphthoic acid in concentrated sulphuric acid at −10° to −5° yields principally 6-nitro-4-keto-1 : 2 : 3 : 4-tetrahydro-2-naphthoic acid.* This substance is readily converted into 6-amino-4-hydroxy-2-naphthoic acid, the carboxylic analogue of the technically important γ-acid, by bromination, dehydrobromination, and subsequent reduction of the nitro-group.

ALTHOUGH the aminonaphtholsulphonic acids represent one of the most important types of intermediate in dye chemistry, very few members of the corresponding series bearing carboxyl in place of the sulphonic acid groups, *i.e.*, aminohydroxynaphthoic acids, are known. The majority of those which have been described in the literature have the hydroxyl and amino-groups situated in the same ring of the naphthalene molecule, whereas those aminonaphtholsulphonic acids which have proved of greatest interest are derived from heteronuclear aminonaphthols.

Aminonaphtholsulphonic acid γ ["γ-acid" (I)] is typical of the class in which the hydroxyl



(I.)



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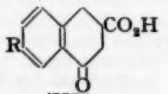

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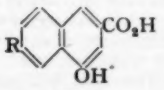

(IV.)

and amino-groups are situated in different rings, and is a substance of great technical importance. It is clear that the synthesis of the carboxylic analogue (IV; R = NH_2) of γ-acid or the synthesis of any other acid with heteronuclear hydroxyl and amino-groups must differ fundamentally from that employed for the corresponding sulphonic acid, as it is not possible to introduce carboxyl groups into β-naphthylamine by any process strictly analogous to that of sulphonation. Moreover, the conversion of a sulphonic acid into a hydroxyl group by alkali fusion, a reaction frequently employed in preparing aminonaphtholsulphonic acids, has no counterpart in the carboxylic acid series.

The methods available for preparing substituted 4-hydroxy-2-naphthoic acids have been discussed by Haworth, Jones, and Way (*J.*, 1943, 10), who conclude that the best general synthesis is that in which a benzylsuccinic anhydride (II) is subjected to ring-closure, the resulting 4-keto-1 : 2 : 3 : 4-tetrahydro-2-naphthoic acid (III) being subsequently converted into a 4-hydroxy-2-naphthoic acid (IV) by successive bromination and dehydrobromination. The benzylsuccinic acids required for this synthesis were obtained by condensing benzyl halides with ethyl sodio-α-acetosuccinate, but, since Haworth *et al.* were unable to obtain 4-nitrobenzylsuccinic acid by this method, they failed to obtain 6-nitro-4-hydroxy-2-naphthoic acid (IV; R = NO_2).

* Patent protection pending.

Ring-closure of 4-nitrobenzylsuccinic anhydride would probably be difficult to achieve on account of the deactivating effect of the nitro-group, but, since this obstacle might be overcome by previous reduction and acetylation, *i.e.*, ring closure of (II; R = NHAc), the condensation of 4-nitrobenzyl chloride with ethyl sodio-α-acetosuccinate was re-investigated (cf. Haworth *et al.*, *loc. cit.*), but without success. Attempts to obtain the required substance by successive condensation of 4-nitrobenzyl chloride with ethyl sodioacetoacetate and ethyl chloroacetate in ethanol, followed by hydrolysis, did not give 4-nitrobenzylsuccinic acid.

The direct nitration of 4-keto-1 : 2 : 3 : 4-tetrahydro-2-naphthoic acid (III; R = H), however, offers a method of preparation for 6-nitro-4-keto-1 : 2 : 3 : 4-tetrahydro-2-naphthoic acid in which the difficulties discussed above are avoided. This substance is smoothly nitrated in concentrated sulphuric acid at −10° to −5°, a 95% yield of crude mononitration product, probably a mixture of 6- and 8-nitro-4-keto-1 : 2 : 3 : 4-tetrahydro-2-naphthoic acid, being obtained. Several recrystallisations of this mixture from water yielded *6-nitro-4-keto-1 : 2 : 3 : 4-tetrahydro-2-naphthoic acid* (III; R = NO_2). Bromination in chloroform then gave *3-bromo-6-nitro-4-keto-1 : 2 : 3 : 4-tetrahydro-2-naphthoic acid*, which was readily dehydrobrominated to *6-nitro-4-hydroxy-2-naphthoic acid* (IV; R = NO_2) by heating it with diethylaniline. Reduction of this nitro-compound with hydrogen at room temperature and pressure in the presence of Raney nickel afforded *6-amino-4-hydroxy-2-naphthoic acid* (IV; R = NH_2), the carboxylic analogue of γ-acid.

Oxidation of 6-nitro-4-keto-1 : 2 : 3 : 4-tetrahydro-2-naphthoic acid with alkaline permanganate gave 4-nitrophthalic acid, from which it is evident that the nitro-group is in position 6 or 7. In order to establish the position of this group with certainty, 6-amino-4-hydroxy-2-naphthoic acid was diazotised and the diazonium solution treated with cuprous chloride. The product, *6-chloro-4-hydroxy-2-naphthoic acid*, was decarboxylated by heating it with quinoline in the presence of copper bronze, the chloronaphthol thus obtained being identical with an authentic sample of 7-chloro-1-naphthol. The latter was prepared from 8-nitro-2-naphthylamine (Saunders and Hamilton, *J. Amer. Chem. Soc.*, 1932, **54**, 638) by diazotisation and the Sandmeyer reaction, yielding 7-chloro-1-nitronaphthalene, reduction of which afforded 7-chloro-1-naphthylamine; this was converted into 7-chloro-1-naphthol by boiling the diazonium salt with 50% sulphuric acid.

Experimental.

(Analyses by Mr. E. S. Morton. M. p.s are uncorrected.)

Benzylsuccinic Acid.—The following method gave a somewhat higher yield than that of Haworth *et al.* (*loc. cit.*) and is more convenient for large-scale preparations. A solution of ethyl sodioacetoacetate, prepared from sodium (115 g.) in ethanol (1375 c.c.) and ethyl acetoacetate (1300 g.), was treated with benzyl chloride (633 g.) at 25—30° and the reaction mixture subsequently boiled under reflux until neutral to litmus. Fractionation in a vacuum, after removal of sodium chloride and ethanol, gave ethyl acetoacetate and ethyl benzylacetoacetate (890 g.), b. p. 136°/2 mm. The latter product (110 g.) was added to a solution of sodium (11·5 g.) in ethanol (150 c.c.), and ethyl chloroacetate (65 g.) run in at 25—30°. After the mixture had been heated under reflux until neutral to litmus, sodium chloride and ethanol were removed. Fractionation in a vacuum yielded ethyl α-aceto-α-benzylsuccinate (82 g.), b. p. 170—180°/1·3 mm. Hydrolysis by boiling 2N-sodium hydroxide (3 mols.) for 18 hours and subsequent acidification then afforded benzylsuccinic acid (80%), which was purified by recrystallisation from hot water; m. p. 160°.

Benzylsuccinic Anhydride (II; R = H).—Benzylsuccinic acid was heated under reflux with an equal weight of acetic anhydride for 15 minutes; acetic acid and excess of anhydride were then removed by distillation. Vacuum distillation of the residue afforded benzylsuccinic anhydride, m. p. 95—97° (90—95%), b. p. 185°/2 mm.

4-Keto-1 : 2 : 3 : 4-tetrahydro-2-naphthoic Acid (III; R = H).—Benzylsuccinic anhydride (100 g.) was added to aluminium chloride (143 g.), dissolved in nitrobenzene (500 c.c.), the temperature being kept at 20—25° (ice-bath). After 24 hours at ordinary temperature, the solution was poured on a mixture of ice and hydrochloric acid. Removal of the nitrobenzene by steam-distillation yielded crude 4-keto-1 : 2 : 3 : 4-tetrahydro-2-naphthoic acid, which was purified by crystallisation from hot water. This method is more convenient than that of Haworth *et al.* for large-scale work.

6-Nitro-4-keto-1 : 2 : 3 : 4-tetrahydro-2-naphthoic Acid (III; R = NO_2).—The foregoing acid (38 g.) was dissolved in sulphuric acid (190 c.c., *d* 1·84) at 10°. A mixture of nitric acid (14·4 c.c.; *d* 1·4) and sulphuric acid (30 c.c., *d* 1·84) was dropped into the stirred solution at −10° to −5°. After being stirred for 1 hour at 0° the reaction mixture was poured on ice, and the product (44·5 g.) collected, washed with water until free from acid, and dried at 50°. Several crystallisations of this crude product, m. p. 154—163°, from hot water gave *6-nitro-4-keto-1 : 2 : 3 : 4-tetrahydro-2-naphthoic acid* (24 g.), m. p. 179° (Found: C, 56·2; H, 4·0; N, 6·2. $C_{11}H_9O_5N$ requires C, 56·15; H, 3·85; N, 5·95%).

Permanganate Oxidation of 6-Nitro-4-keto-1 : 2 : 3 : 4-tetrahydro-2-naphthoic Acid.—The nitro-compound (1·1 g.) in a slight excess of dilute sodium carbonate solution was treated with potassium permanganate (4 g.; 2·5% solution) at the boil. When oxidation was complete, the solution was filtered from manganese dioxide, and the filtrate concentrated to 50 c.c., acidified with concentrated hydrochloric acid, and extracted with ether (2 × 25 c.c.). After removal of the ether, the residue was

heated under reflux with acetic anhydride (2 c.c.) for 5 minutes, and the latter then removed under reduced pressure. Sublimation under 2 mm. pressure and crystallisation of the sublimate from benzene–ligroin yielded 4-nitrophthalic anhydride, m. p. 119°, not depressed by admixture with an authentic sample.

3-Bromo-6-nitro-4-keto-1 : 2 : 3 : 4-tetrahydro-2-naphthoic Acid.—6-Nitro-4-keto-1 : 2 : 3 : 4-tetrahydro-2-naphthoic acid (20 g.), suspended in chloroform (60 c.c.), was treated gradually with a solution of bromine (4·6 c.c.) in chloroform (40 c.c.). The reaction mixture was warmed to 40° after addition of the first portion of bromine solution to initiate the reaction and then instantly cooled to 15°, the remainder of the bromine being added at 15—20°. After removing the solvent in a vacuum, the crude *bromo*-compound (22·5 g.) was purified by crystallisation from acetone–benzene. It then melted at 188°, with evolution of hydrogen bromide (Found : C, 42·5; H, 2·85; Br, 24·8. $C_{11}H_8O_5NBr$ requires C, 42·05; H, 2·55; Br, 25·4%).

6-Nitro-4-hydroxy-2-naphthoic Acid (IV; R = NO_2).—The foregoing bromo-compound (26 g.) and diethylaniline (260 c.c.) were heated on the steam-bath for 6 hours. After addition of excess of sodium hydrogen carbonate, the diethylaniline was removed by steam-distillation, and the residual solution poured into an excess of 2N-hydrochloric acid. The solid product (18·2 g.) was collected, washed with water, and dried at 50°. It was dissolved in ethanol, and the resulting solution clarified (carbon) and evaporated to dryness. Crystallisation of the residue from acetone yielded *6-nitro-4-hydroxy-2-naphthoic acid* as orange prisms (Found : C, 56·8; H, 3·3; N, 6·2. $C_{11}H_7O_5N$ requires C, 56·65; H, 3·0; N, 6·0%).

6-Amino-4-hydroxy-2-naphthoic Acid (IV; R = NH_2).—6-Nitro-4-hydroxy-2-naphthoic acid (25 g.) and Raney nickel catalyst (*ca.* 2 g.) (prepared as described below) in ethanol (350 c.c.) were shaken with hydrogen at room temperature and pressure. When absorption of hydrogen had ceased, the catalyst was filtered off, and the filtrate immediately added to 10N-hydrochloric acid (15 c.c.) mixed with ethanol (40 c.c.). The ethanol was removed in a vacuum, the residual solid (25 g.) dissolved in warm 0·1N-hydrochloric acid (50 c.c.), and the solution clarified (carbon) and cooled to 10°. Addition of an equal volume of concentrated hydrochloric acid precipitated *6-amino-4-hydroxy-2-naphthoic acid hydrochloride*, which was dried in a vacuum (NaOH) (Found : C, 55·35; H, 4·5; N, 6·4; Cl, 14·85. $C_{11}H_9O_3N$,HCl requires C, 55·1; H, 4·2; N, 5·9; Cl, 14·8%). Cautious addition of dilute aqueous ammonia to an aqueous solution of the hydrochloride yielded the free *amino-acid* as a cream-coloured precipitate which darkened in air (Found : C, 65·45; H, 4·5; N, 7·3. $C_{11}H_9O_3N$ requires C, 65·05; H, 4·45; N, 6·9%).

6-Chloro-4-hydroxy-2-naphthoic Acid (IV; R = Cl).—6-Amino-4-hydroxy-2-naphthoic acid hydrochloride (2·5 g.) was dissolved in water (10 c.c.) and 10N-hydrochloric acid (2·5 c.c.) by warming, and diazotised at 0° by addition of 2N-sodium nitrite (5 c.c.) with stirring. The diazonium salt suspension was added to cuprous chloride (1·2 g.) in hydrochloric acid (20 c.c., *d* 1·18), and the reaction mixture stirred for 1 hour at 20°, after which the temperature was raised to 80° during 15—30 minutes. After cooling, the product was filtered off and dissolved in dilute sodium carbonate, and the clarified (carbon) solution poured into an excess of dilute hydrochloric acid. Crystallisation from methanol gave the *acid*, m. p. 302—304° (Found : Cl, 16·1. $C_{11}H_7O_3Cl$ requires Cl, 15·95%).

Decarboxylation of 6-Chloro-4-hydroxy-2-naphthoic Acid.—The acid (0·5 g.) was heated under reflux with quinoline (5 c.c.) and copper bronze (0·5 g.) for 2½ hours, and, after the mixture had been cooled, 5N-sodium hydroxide (10 c.c.) was added. After removal of the quinoline by steam-distillation, the liquors were concentrated to 40—50 c.c., clarified (carbon), and treated with carbon dioxide until precipitation was complete. The precipitate was collected and re-dissolved in 0·2N-sodium hydroxide (5 c.c.), the solution filtered, and the filtrate poured into an excess of 2N-hydrochloric acid. The product, purified by crystallisation from hot water, had m. p. 120—121°, not depressed by admixture with an authentic sample of 7-chloro-1-naphthol.

7-Chloro-1-nitronaphthalene.—A solution of 8-nitro-2-naphthylamine (Saunders and Hamilton, *loc. cit.*) (9·4 g.) in glacial acetic acid (50 c.c.) was added to sodium nitrite (3·5 g.) in sulphuric acid (50 c.c., *d* 1·84) with stirring, the temperature being kept at 15—25° (ice bath). After a further 15 minutes the diazonium salt solution was added with stirring to a solution of cuprous chloride (23·5 g.) in hydrochloric acid (190 c.c., *d* 1·18). After 1 hour, water (470 c.c.) was added, and the product collected and dried at 50°. It was purified by crystallisation from ethanol (carbon); yield, 4·8 g.; m. p. 112° (lit., m. p. 116°).

7-Chloro-1-naphthylamine.—Raney nickel catalyst (1 g.) was added to 7-chloro-1-nitronaphthalene (4·16 g.) in ethanol (200 c.c.). Reduction was effected by shaking with hydrogen at room temperature and pressure until absorption ceased. After removal of the catalyst and the ethanol, the residue was added to an excess of 10N-hydrochloric acid. The hydrochloride of 7-chloro-1-naphthylamine (m. p. 258°) separated on cooling (Schroeter, *Ber.*, 1930, **63**, 1318, gives m. p. 235—239°).

7-Chloro-1-naphthol.—7-Chloro-1-naphthylamine (as hydrochloride, 4·28 g.) was diazotised at 0—5° in sulphuric acid (3 c.c., *d* 1·84) and water (20 c.c.) by addition of 2N-sodium nitrite (10 c.c.). The diazonium salt solution was added dropwise to boiling sulphuric acid (150 c.c.; 50% w/w), the product being simultaneously removed by steam-distillation. The aqueous distillate was cooled and the product collected. It was purified by crystallisation from hot water, m. p. 121—122° (lit., m. p. 123°).

Raney nickel catalyst. Catalyst, of activity suitable for the above reactions, was prepared as follows. 11N-Sodium hydroxide (270 c.c.) and water (360 c.c.) were heated to 50° and Raney nickel alloy (150 g.) added during 2 hours with stirring, the temperature being kept below 98°. More 11N-sodium hydroxide (100 c.c.) and water (50 c.c.) were added and the temperature raised to 115°. After 4 hours at 115°, the mixture was cooled, and the catalyst washed twice by decantation, filtered, and washed with water (4 l.) on the filter.

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403. *Studies in Light Absorption. Part VI. Steric Inhibition of Resonance in Natural and Synthetic Derivatives of* cyclo*Hexene.*

By E. A. Braude, E. R. H. Jones, H. P. Koch, R. W. Richardson, F. Sondheimer, and J. B. Toogood.

1-Acetyl-2-methyl*cyclo*hexene as prepared by two different methods is shown to be a mixture of the Δ^1- and the Δ^2-isomer, which can be separated either by fractional distillation or through the semicarbazones. No indication of the presence of the unconjugated isomer was obtained with acetyl*cyclo*hexene.

The ultra-violet light absorption properties of 1-acetyl-2-methyl*cyclo*hex-1-ene, β-ionone, dehydro-β-ionone, β-irone, and certain related synthetic compounds are uniformly anomalous in that the intensities of the bands characteristic of the conjugated systems are much lower than for the open-chain analogues. This anomaly is not exhibited by the unsubstituted cyclic homologues and is ascribed to steric inhibition of resonance, the unsaturated side-chain being displaced out of the plane of the *cyclo*hexene ring by the neighbouring methyl groups. The effect is similar to that previously observed by Rodebush and others in *o*-methylacetophenones and related aromatic systems. The general principles underlying the interpretation of steric effect on electronic spectra are discussed and applied qualitatively to the parent compounds named above and to some of their carbonyl derivatives.

The work described in this paper was initiated about eight years ago as a result of the observation, briefly discussed in two earlier publications (Koch, *Chem. and Ind.*, 1942, **61**, 273; Braude, Jones, Sondheimer, and Toogood, this vol., p. 607) that 1-acetyl-2-methyl*cyclo*hex-1-ene (I) exhibits ultra-violet light absorption of the expected wave-length but of much lower intensity than that to be expected by analogy with acetyl*cyclo*hexene (a; this and other letters in parentheses refer to the table on p. 1892) and acylic αβ-unsaturated ketones. This apparent anomaly can be satisfactorily explained (see below) in terms of steric interference between the acetyl group and the methyl substituent, and it seemed very probable that an analogous effect was responsible for the anomalous light absorption of certain other conjugated side-chain derivatives of *cyclo*hexene, particularly β-ionone and related compounds. Partly in order to test this hypothesis and partly in view of their potentialities as intermediates in the synthesis of vitamin A analogues, a range of suitable compounds of this type differing in the extent of alkyl substitution has now been prepared (Heilbron, *J.*, 1948, 386; Heilbron, Jones, Richardson, and Sondheimer, this vol., p. 737; Heilbron, Jones, Toogood, and Weedon, this vol., p. 1827), and their spectral properties together with those of some of their derivatives are described and discussed in the present communication.

The data are collected in the table. Acetyl*cyclo*hexene (a) exhibits a band with $\lambda_{max.}$ 2320 A., $\varepsilon_{max.}$ 12,500, entirely analogous to that shown by open-chain αβ-unsaturated ketones with αβ-alkyl substitution (Woodward, *J. Amer. Chem. Soc.*, 1941, **63**, 1123; 1942, **64**, 76; Evans and Gillam, *J.*, 1941, 815). 1-Acetyl-2-methyl*cyclo*hexene, as prepared by the reaction of 1-methyl-*cyclo*hexene with acetyl chloride in the presence of stannic chloride (Ruzicka, Koolhaas, and Wind, *Helv. Chim. Acta*, 1931, **14**, 1151; Huber, *Ber.*, 1938, **71**, 725) as well as by the rearrangement of 2-methyl-1-ethynyl*cyclo*hexanol with formic acid (cf. Hurd and Christ, *J. Amer. Chem. Soc.*, 1937, **59**, 118; Chanley, *ibid.*, 1948, **70**, 244), exhibited a maximum at 2450 A., $\varepsilon_{max.}$ 4000—5000, corresponding to the wave-length displacement expected for the change from αβ-dialkyl to αββ-trialkyl substitution, but also an unexpected decrease in intensity. Moreover, the intensity values differed somewhat in different preparations, and the material obtained by either method proved to be a mixture of the Δ^1-isomer (I) and the less-absorbing Δ^2-isomer (II), which were separated by fractional distillation (b. p.s 89°/12 mm. and 79°/12 mm., respectively).

(I.) (II.)

Separation was effected also by fractional crystallisation of the semicarbazones (m. p.s 213° and 132°, respectively). No isomerisation appears to accompany the regeneration of the parent ketones by means of phthalic anhydride or cold dilute sulphuric acid, but the semicarbazone of (II) is converted quantitatively into (I) when distilled in steam in the presence of oxalic acid. A careful examination of acetyl*cyclo*hexene (a), prepared by the rearrangement of ethynyl*cyclo*-hexanol with formic acid, failed to yield any evidence of the presence of the corresponding Δ^2-isomer. The prototropic isomerism exhibited by acetylmethyl*cyclo*hexene is closely reminiscent of the behaviour of other alkylated *cyclo*hexene derivatives such as *cyclo*citral,

ionone, and irone, all of which are well known to exist in two so-called β- (Δ^1-) and α- (Δ^3-)forms, readily interconvertible in the presence of suitable catalysts (cf. Köster, *Ber.*, 1944, **77**, *B*, 553; Andrews, Cristol, Lindenbaum, and Young, *J. Amer. Chem. Soc.*, 1945, **67**, 715; Young and Linden, *ibid.*, 1947, **69**, 2072; Ruzicka, Seidel, Schinz, and Tavel, *Helv. Chim. Acta*, 1948, **31**, 257). It is interesting that the experimental details recorded by Evans and Gillam (*loc. cit.*) for the preparation and light absorption of 3 : 4-dimethylpent-3-en-2-one (III; $R_1 = R_2 = Me$), an acyclic analogue of acetylmethyl*cyclo*hexene, also indicate that the compound is obtained as a mixture of the αβ- and βγ-isomers (III and IV). Again, the lower homologue mesityl oxide (III; $R_1 = Me$, $R_2 = H$) as prepared in the ordinary way has been shown to contain *ca.* 10%

$CH_3 \cdot CR_1 : CR_2 \cdot CO \cdot CH_3$ (III.) $CH_2 : CR_1 \cdot CHR_2 \cdot CO \cdot CH_3$ (IV.)

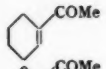
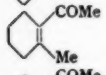
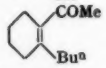
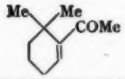
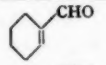
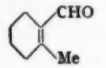
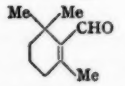
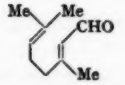
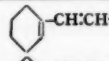
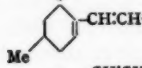
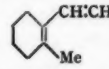
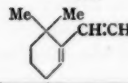
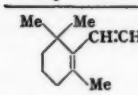
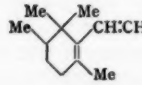
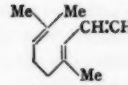
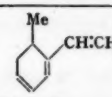
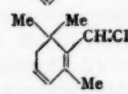
of the βγ-isomer (Stross, Monger, and Finch, *J. Amer. Chem. Soc.*, 1947, **69**, 1627; Gray, Rasmussen, and Tunnicliff, *ibid.*, p. 1630). Ethylideneacetone (III; $R_1 = R_2 = H$), an open-chain analogue of acetyl*cyclo*hexene, does not appear to have been examined in this respect, but the relatively low ε value which has been recorded (Evans and Gillam, *loc. cit.*) suggests that the non-absorbing βγ-isomer may be present also in this case.

Pure 1-acetyl-2-methyl*cyclo*hex-1-ene (b), obtained in the way described above, still exhibits a maximum of abnormally low intensity (ε 6500), in agreement with the data for material prepared by a different route (Braude, Jones, Sondheimer, and Toogood, *loc. cit.*). 1-Acetyl-2-*n*-butyl*cyclo*hexene (c) (*idem, ibid.*) exhibits a maximum of identical location, but of even lower intensity than the methyl homologue. On the other hand, no appreciable lowering in intensity is observed in 1-acetyl-6 : 6-dimethyl*cyclo*hexene (d) (Chanley, *J. Amer. Chem. Soc.*, 1948, **70**, 244), and the anomalous effect is thus produced only when an alkyl substituent occurs in the 2-position.

*cyclo*Hexenealdehyde (e), just as acetyl*cyclo*hexene, exhibits quite normal light absorption, and introduction of a 2-methyl substituent (in f) again leads to the increase in $\lambda_{max.}$ expected for the change from αβ- to αββ-alkyl substitution (cf. Evans and Gillam, *J.*, 1943, 565); no appreciable decrease in intensity is observed in this case and $\varepsilon_{max.}$ remains of the same order as in the acyclic citral (h). β-*cyclo*Citral (g), which contains two additional 6-methyl substituents was originally reported (Burawoy, *J.*, 1941, 20) to absorb with abnormally low intensity, but more recent work by Young and Linden (*loc. cit.*) shows that this was probably due to admixture with the α-isomer, and that pure β-*cyclo*citral, prepared by regeneration from the semicarbazone with sulphuric acid in the cold, has an $\varepsilon_{max.}$ value almost identical with that of *cyclo*hexenealdehyde and 2-methyl*cyclo*hexenealdehyde. Thus methyl substituents in either the 2- or the 6-position are practically without influence on the intensity of the characteristic band in the *cyclo*hexenealdehyde system.

In *cyclo*hexene derivatives containing the side-chain $-CH:CH \cdot CO \cdot Me$, *e.g.*, in the series consisting of the β-ionone lower homologues (i), (j), (k), and (l), β-ionone (m), and β-irone (n), as well as in the dehydro-derivatives (p) and (q), yet a different behaviour is encountered. A 2-methyl substituent again displaces the position of the absorption maximum of the dienone system by *ca.* 150 A., but $\varepsilon_{max.}$ is almost unchanged. Introduction of a 6-*gem.*-dimethyl group, however, reduces $\varepsilon_{max.}$ by half; thus, the β-ionone homologue (l), β-ionone and β-irone, unlike β-*cyclo*citral, all exhibit characteristic long-wave-length bands of abnormally low intensity even after the most careful exclusion of the α-isomers. At the same time additional short-wave-length bands near 2200 A. appear. In ψ-ionone (o), in which the *cyclo*hexene ring is opened, the intensity of the band at 2900 A. regains its normal value and no band is observed at 2200 A.

The differing influence of 2- and 6-alkyl substituents in the three systems is again brought out in the light absorption of the semicarbazones and 2 : 4-dinitrophenylhydrazones of the parent carbonyl compounds. The spectra of these derivatives are also given in the annexed table and need not be described in detail, but may be summarised as follows: (i) The absorption data of the derivatives of the unsubstituted carbonyl compounds are the same as for the derivatives of the corresponding open-chain analogues (cf. Evans and Gillam, *J.*, 1943, 565; Braude and Jones, *J.*, 1945, 498), (ii) the introduction of a methyl substituent which increases $\lambda_{max.}$ without reducing $\varepsilon_{max.}$ of the parent carbonyl compound, has the same effect for the derivative, and (iii) the introduction of a methyl substituent which reduces $\varepsilon_{max.}$ of the parent carbonyl compound, reduces both $\varepsilon_{max.}$ and $\lambda_{max.}$ of the derivative.

		Carbonyl compound.†		Semicarbazone.†		2 : 4-Dinitrophenylhydrazone.‡	
		$\lambda_{max.}$, A.*	$\varepsilon_{max.}$	$\lambda_{max.}$, A.	$\varepsilon_{max.}$	$\lambda_{max.}$, A.	$\varepsilon_{max.}$
(a)		2320	12,500	2600	24,600	3870	27,500
(b)		2450 *2490*	6,500 *6,000*	2330 2420 2510	9,800	3750	24,000
(c)		2450	4,000 [1]	2260	12,000 [1]	3690	25,500 [1]
(d)		2320	12,000 [2]	2550	15,600 [2]		
(e)		2290	12,100 [3]	2600 2650	28,500 [3] 31,700	3770	27,800 [3]
(f)		2420 2510	11,200 [3]	2740 *2800*	23,200 [3] *21,700*	3870	29,500 [3]
(g)		2490	11,600 [4]	2730	24,500 [5]	3890	28,000 [6]
(h)		2380	13,500 [7]	2720	31,400 [7]	3850	3,1000 [6]
(i)		2810	20,800 [3]	2900 *3000*	35,000 [3] *32,000*	3950	32,000 [3]
(j)		2790 2730	23,000 23,000	2910 3000	37,000 32,000	3930	34,500
(k)		2200 2960	4,000 [3] 20,300	3030	40,900 [3] ‡	4020	39,900 [3]
(l)		2280 2810 *2900*	4,100 [8] 13,000 12,500	2820 2910	29,500 30,500	3920	31,000
(m)		2230 2960	6,500 [9] 10,700	2820	22,300 [9]	3880	27,500 [6]
(n)		2950	11,200 [10]				
(o)		2910	21,800 [7]	3000	45,400 [7]	4070	34,500 [5]
(p)		3370	17,700 [3]	2550 3190 3340 3500	13,200 [3] 19,100 25,000 20,200	4120	34,900 [3]
(q)		2210 3380	7,200 [11] 9,100	2600 3150 *3240*	12,400 [11] 16,500 *16,000*	3980 and 4050	27,800 [11] and 28,900

* Data in italics refer to inflexions. † In ethanol. ‡ In chloroform.

[1] Braude, Jones, Sondheimer, and Toogood, this vol., p. 607. [2] Chanley, *J. Amer. Chem. Soc.*, 1948, **70**, 244. [3] Heilbron, Jones, Richardson, and Sondheimer, this vol., p. 737. [4] Young and Linden, *J. Amer. Chem. Soc.*, 1947, **69**, 2072. [5] Andrews, Cristol, Lindenbaum, and Young, *ibid.*, 1945, **67**, 715. [6] Braude and Jones, *J.*, 1945, 498. [7] Burawoy, *J.*, 1941, 20. [8] Heilbron, Jones, Toogood, and Weedon, this vol., p. 1827. [9] Young, Cristol, Andrews, and Lindenbaum, *J. Amer. Chem. Soc.*, 1944, **66**, 855 (data for shorter-wave-length band of β-ionone determined by present authors). [10] Ruzicka, Seidel, Schinz, and Tavel, *Helv. Chim. Acta*, 1948, **31**, 257; Naves, *ibid.*, p. 893. [11] Henbest, *Nature*, 1948, **161**, 481, and private communication. [12] Naves and Ardizio, *Helv. Chim. Acta*, 1949, **32**, 1228.

Discussion.

The abnormal light-absorption properties of β-ionone and its semicarbazone were first noted by Burawoy (*loc. cit.*) who ascribed the low intensity values to a " ring-closure effect " and the low value of $\lambda_{max.}$ of the semicarbazone to a " steric-hindrance effect " of the methyl groups. However, the data now available show that ring closure as such evidently does not lead to any reduction in intensity since *cyclo*hexenealdehyde, acetyl*cyclo*hexene, and the β-ionone homologues (i), (j), and (k) all exhibit absorption of the same intensity as their acyclic analogues, and there is no obvious reason why steric hindrance should be operative in the semcarbazone and not in the parent carbonyl compound.

Many examples of the effects of steric factors on electronic spectra have been described, relating mostly to aromatic systems. They fall into three categories: (*a*) differences in light absorption between *cis*- and *trans*-isomers, *e.g.*, in the stilbenes, cinnamic acids, azobenzenes, and carotenoids (Smakula and Wasserman, *Z. physikal. Chem.*, 1931, *A*, **155**, 353; Cook, Jones, and Polya, *J.*, 1939, 1315; Zechmeister, *Chem. Reviews*, 1944, **34**, 267); (*b*) large changes in light absorption consequent upon the introduction of substituents normally producing only small spectral effects, but in positions where they may be expected to decrease the planarity of the conjugated system, *e.g.*, in *o*-methyl-diphenyls, -styrenes, -stilbenes, -acetophenones, and -dialkylanilines (Pickett, Walter, and France, *J. Amer. Chem. Soc.*, 1936, **58**, 2296; Rodebush *et al.*, *ibid.*, 1940, **62**, 2906; 1941, **63**, 3018; 1946, **68**, 896; Carlin and Constantine, *ibid.*, 1947, **69**, 50; Remington, *ibid.*, 1945, **67**, 1838); and (*c*) lack of spectral interaction, in large molecules, between conjugated chromophores expected to be non-coplanar, *e.g.*, in certain polyarylethylenes and diaryls (Jones, *J. Amer. Chem. Soc.*, 1941, **63**, 1658; 1943, **65**, 1818; 1945, **67**, 2127; *Chem. Reviews*, 1947, **41**, 353; Friedel, Orchin, and Reggel, *J. Amer. Chem. Soc.*, 1948, **70**, 199).

The present observations are clearly of the type described under (*b*) and there can be little doubt that the abnormalities observed are mainly steric in origin and that they arise through the displacement of the unsaturated side-chains out of the plane of the *cyclo*hexene ring owing to interference with the methyl substituents.

It is now well recognised that the near-ultra-violet and visible light absorption of conjugated systems is closely related to the occurrence of valence-bond resonance (for references see Pauling in Gilman, " Organic Chemistry," Wiley, 1943; Braude, *Ann. Reports*, 1945, **42**, 105; Maccoll, *Quart. Reviews*, 1947, **1**, 16) and that an essential requirement for maximum resonance is a co-planar configuration of all the bonds concerned. The relations which might, however, be expected between steric inhibition of resonance and electronic spectra have been variously interpreted and the following is an attempt to restate the basic principles involved.

(i) Light absorption in the near ultra-violet region can be regarded as resulting in transitions from a hybrid ground state, to which resonance forms (particularly ionic resonance forms) of higher energy content than classical structures make a relatively small contribution, to excited states to which resonance forms of higher energy content make a larger contribution.

(ii) A structural change which increases the conjugation and thereby lowers the energy content of the higher resonance forms will normally decrease the energy of the excited state more than that of the ground state (since the contribution of non-classical resonance forms is greater in the excited than in the ground state) and therefore decrease the excitation energy; *i.e.*, this change increases the wavelength associated with the electronic transition. Differences in the light absorption of *cis*- and *trans*-isomers will be at least partly of this type (quite independently of any steric interference in the *cis*-form) since the actual configuration of the chromophore is different in the two cases.

(iii) A structural change which tends to decrease the planarity of the conjugated system might be expected to influence ultra-violet absorption properties in the following ways. If the steric interference resulting in non-planarity is relatively small, then the characteristic transition of the chromophore might be restricted to vibrational states in which appropriate bonds are sufficiently extended to allow of a large degree of co-planarity. Solution spectra representing band envelopes rather than discrete bands will then show little change in wave-length location, but the intensity of absorption will be decreased since the transition will be restricted to a smaller number of vibrational states. At the same time, bands characteristic of the partial chromophore present in the non-planar configuration will appear, increasing in intensity as the intensity of the main band decreases. If, however, steric interference is large and resonance interaction takes place despite non-planarity, the energy content of the contributing resonance forms will be increased and the energy level of the excited state will therefore be raised relatively to that of the ground state; *i.e.*, the characteristic band itself will be displaced towards shorter wave-lengths. If the expected wave-length locations of the full and partial chromophore

bands do not lie far apart, *e.g.*, in multiple conjugated systems, it will not always be a simple matter to decide between the two interpretations.

The present observations appear to receive satisfactory explanation in terms of the principles formulated above. Dealing first with the parent carbonyl compounds, it will be noted that the wave-length locations of the maxima in any one group bear no direct relation to the intensities, but are constant in the absence of 2-alkyl substituents and uniformly displaced by *ca.* 150 A. towards higher wave-lengths in their presence. These displacements can therefore be regarded as simple bathochromic effects due to the interaction of the alkyl groups with the conjugated system, entirely analogous to the effect observed with acyclic ethylenic carbonyl compounds (Woodward, *loc. cit.*; Evans and Gillam, *loc. cit.*).

In the *cyclo*hexenealdehydes, the intensities are practically unaffected by 2- or 6-methyl substituents, and any steric interference between the methyl and the aldehyde groups is therefore not sufficiently great to be manifested in the light-absorption properties. On examining scale models, it is found that, in configurations in which the aldehyde group is co-planar with the *cyclo*hexene ring, the distance between the oxygen atom and the methyl substituents is considerably smaller than the sum of the van der Waals radii, but slightly larger than the sum of the covalent radii. It is now generally accepted that van der Waals radii are probably too large a measure of the intra-molecular interference properties of atoms. On the other hand, covalent radii, though almost certainly too small, represent a reliable measure of the ***minimum*** interference properties of non-bonded atoms and appear to afford a better indication of the degree of interference necessary to produce anomalous ultra-violet-light absorption properties, possibly because a certain extent of non-planarity can be tolerated before resonance is seriously inhibited. Projections of the two co-planar *s-cis*- and *s-trans*-configurations * of β-*cyclo*citral, employing covalent radii, are shown in Figs. 1*a* and 1*b*. It will be seen that no overlap between the aldehyde group and either the 2- or 6-methyl substituents is apparent on this basis.

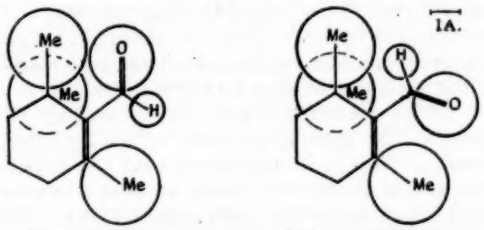
The corresponding scale diagrams for acetylmethyl*cyclo*hexene are shown in Figs. 2*a* and 2*b*. No overlap occurs in the *s-cis*-configuration but, as a result of the replacement of the aldehyde by an acetyl group, interference is indicated in the *s-trans*-configuration between the acetyl-methyl group and the 2-methyl substituent. Similarly, the diagrams (Figs. 3*a* and 3*b*) for 6 : 6-dimethylacetyl*cyclo*hexene indicate intereference for the co-planar *s-cis*- but not for the *s-trans*-configuration of this compound. The fact that an intensity reduction of the band characteristic of the enone system is shown by the 2-methyl but not by the 6 : 6-dimethyl derivative would therefore appear to suggest that in both compounds the *s-trans*-configuration is preferred. This is in harmony with the fact that, in general, the most elongated configuration of a conjugated system appears to be the most stable; thus, butadiene is believed to exist predominantly in the *s-trans*-configuration at room temperature, and the energies of the ground levels of the *s-trans*- and *s-cis*-forms are thought to differ by as much as 6 kcals./mol. (Mulliken, *J. Chem. Physics*, 1939, **7**, 121; Sugden and Walsh, *Trans. Faraday Soc.*, 1945, **41**, 76). This difference is of the same order of magnitude as that found with stable *cis*- and *trans*-isomers about ethylenic bonds. The fact that the only variations in wave-length location of the maxima in the *cyclo*hexene-aldehydes and acetyl*cyclo*hexenes are those to be expected from the differences in alkyl substitution supports the tentative conclusion that all these compounds tend to assume identical *s-trans*-configurations. This conclusion, if correct, implies that in the case of acetyl-methyl*cyclo*hexene and other acetyl-2-alkyl*cyclo*hexenes the preference for the *s-trans*-configuration over the *s-cis*-configuration outweighs the steric hindrance to co-planarity in the former. The potential energy difference between the *s-cis*- and *s-trans*-forms might be expected to be of the same order as in butadiene, *i.e.*, *ca.* 5—6 kcals./mol., so that the steric hindrance effect, which would have to be smaller than this, could amount to, at most, *ca.* 4 kcals./mol. It was pointed out in the general discussion (p. 1893) that steric interference, if relatively small, might be expected to produce only decreases in intensity without any wave-length displacements. The acetyl-2-alkyl*cyclo*hexenes and the ionones discussed below appear to be examples of this type (an energy difference of 4 kcals./mol. corresponds to a wave-length displacement of less than 100 A. in this region). The same applies to the related *o*-methyldiphenyls and *o*-methyl-acetophenones (Rodebush *et al.*, *loc. cit.*) which also exhibit intensity reductions without any appreciable changes in the wave-length locations of the maxima.

In the ionones, the number of feasible co-planar configurations is multiplied by the possibility

* The nomenclature employed is that introduced by Mulliken (*Rev. Mod. Physics*, 1942, **14**, 265) for distinguishing between geometrical isomers about conventional single bonds which possess some double-bond character.

of *cis-trans*-isomerism about the ethylenic bond, and of *s-cis*- or *s-trans*-orientation about the two carbon–carbon single bonds in the side-chain. A *cis*-configuration of the ethylenic bond in

FIG. 1.

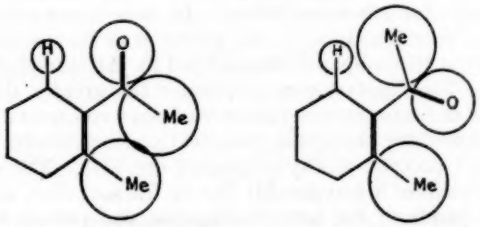


(a) s-trans-*Configuration.* (b) s-cis-*Configuration.*

β-cyclo*Citral.*

Dimensions used in Figs. 1–4 : C—C *bond length* 1·54 A., C=C *bond length* 1·33 A., C—H *bond length* 1·08 A., C=O *bond length* 1·22 A., H *covalent-bond radius* 0·31 A., Me *covalent-bond radius* 1·39 A., =O *covalent-bond radius* 1·10 A.

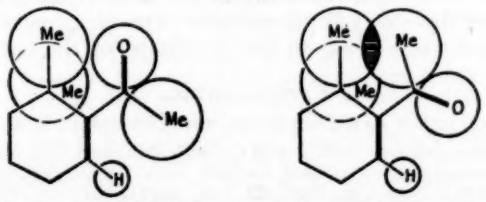
FIG. 2.



(a) s-trans-*Configuration.* (b) s-cis-*Configuration.*

1-*Acetyl*-2-*methyl*cyclo*hexene.*

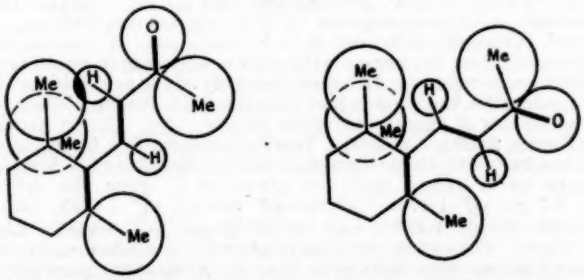
FIG. 3.



(a) s-trans-*Configuration.* (b) s-cis-*Configuration.*

1-*Acetyl*-6 : 6-*dimethyl*cyclo*hexene.*

FIG. 4.



(a) trans-*Configuration.* (b) s-cis-*Configuration.*

β-Ionone.

β-ionone has been advocated (Naves and Bachmann, *Helv. Chim. Acta.*, 1943, **26**, 2153), though on rather ambiguous evidence, and is not incompatible with the method of preparation of the synthetic analogues. It would, however, imply strong steric interference between the acetyl

group and one of the ring-hydrogen atoms in the completely demethylated analogue (i). The intensity and wave-length location of the 2800 A. maximum exhibited by this compound are very similar to those shown by the acyclic ψ-ionone (o), and a *cis*-configuration of the side-chain ethylenic bond therefore appears unlikely. If a *trans*-configuration is assumed for this bond, no interference with the acetyl group is indicated by diagrams employing covalent radii, even in the presence of 2- or 6-methyl substituents. There is, however, a significant overlap between a 6-methyl substituent and a hydrogen atom of the side-chain, provided that the orientation about the single bond between the *cyclo*hexene ring and the side-chain is *s-trans* (Figs. 4*a* and 4*b*). This would be expected to be the preferred orientation by analogy with that suggested for the other diene and enone systems. No overlap is shown with a 2-methyl substituent in either the *s-trans*- or *s-cis*-configurations. This is in agreement with the experimental data which show that a large intensity reduction of the dienone band at 2800 A. is produced by 6-*gem*-dimethyl substituents whilst 2-methyl substituents have only a small effect. The increase in the intensity of the 2200 A. band which is observed also in the former case may be ascribed to the partial enone chromophore in the side-chain (in the case of the acetyl*cyclo*hexenes, the characteristic wave-length bands of the partial $-C=C-$ and $-C=O$ chromophores fall ouside the observational range).

We shall now turn to the semicarbazones and dinitrophenylhydrazones of the parent carbonyl compounds. Increases in $\lambda_{max.}$ due to 2-methyl substituents without changes in $\varepsilon_{max.}$ are clearly simple alkylation effects as before. In those cases where 2-methyl substituents result in a decrease in $\lambda_{max.}$ as well as in $\varepsilon_{max.}$, the positions of the maxima are displaced towards those expected for the partial chromophore represented by the side-chain and not involving the unsaturation in the ring. The displacement is greater the greater the steric interference, as indicated by the intensity decrease in the parent carbonyl compound, and the derivatives of 1-acetyl-2-*n*-butyl*cyclo*hexene show absorption practically identical with that of derivatives of an unconjugated ketone, *e.g.*, 1-acetyl-2-methyl*cyclo*hex-2-ene (II). The decreases in $\lambda_{max.}$ in the sterically " hindered " derivatives is presumably due to the fact that, unlike those in the parent carbonyl compounds, the bands of the fully conjugated and partial side-chain chromophores are situated fairly closely together in wave-length and do not differ greatly in intensity, and that the appearance of the " partial " bands masks the much reduced longer-wave-length bands due to full conjugation. This is borne out by the fact that the bands in the sterically hindered derivatives are unusually wide, and, especially in the semicarbazones, often show subsidiary inflections. In these cases there may be, in addition to purely geometrical superposition, some additional resonance degeneracy owing to the proximity of the energy levels.

Experimental.

(Absorption spectra, unless stated otherwise, were determined in alcoholic solutions).

Condensation of 1-*Methyl*cyclo*hexene with Acetyl Chloride* (Ruzicka, Koolhaas, and Wind, *loc. cit.*).—The reaction was carried out by the recorded method with 1-methyl*cyclo*hexene (130 g.; prepared according to Mosher, *J. Amer. Chem. Soc.*, 1940, **62**, 552), acetyl chloride (106 g.), and stannic chloride (345 g.) in carbon disulphide (825 g.). After treatment with diethylaniline (130 g.), the crude ketone (75 g.; 40% yield) had b. p. 95—100°/23 mm., and on distillation through a Widmer column at 16 mm. the following fractions were collected: (i) b. p. 82—83° (7·5 g.), $n_D^{20°}$ 1·4715; (ii) 83—84° (8·2 g.), $n_D^{20°}$ 1·4715; (iii) 85—86° (3·7 g.), $n_D^{20°}$ 1·4751; (iv) 86—87° (9·2 g.), $n_D^{19°}$ 1·4788; (v) 87—88° (7·0 g.), $n_D^{19°}$ 1·4805; (vi) 88—89° (8·2 g.), $n_D^{18°}$ 1·4832; (vii) 89—90° (4·4 g.), $n_D^{17°}$ 1·4841. Light absorption of (i): Maximum, 2450 A.; ε, 1600. Light absorption of (vii): Maximum, 2450 A.; ε, 5600.

Treatment of 2-*Methyl*-1-*ethynyl*cyclo*hexanol with Formic Acid*.—A solution of 2-methyl-1-ethynyl-*cyclo*hexanol (83 g.; prepared from the ketone with sodium acetylide in liquid ammonia) in formic acid (750 g.; 90%) was heated under reflux for 2½ hours; the bulk of the acid was removed through a column under reduced pressure, and after the residue had been neutralised with sodium carbonate solution the product was isolated by means of ether; the crude ketone (62 g.; 76%) had b. p. 80—90°/11 mm. Light absorption: Maximum, 2450 A.; ε, 4000. Distillation through a fractionating column containing a 40 × 1·5-cm. section packed with single-turn glass halices, fitted with a total condensation variable take-off head operating at a reflux ratio of about 8 : 1, gave the following fractions: (i) b. p. 78—84°/12 mm. (1·7 g.), $n_D^{18°}$ 1·4704; (ii) 84—86° (5·8 g.), $n_D^{18°}$ 1·4783; (iii) 86—88° (9·2 g.), $n_D^{18°}$ 1·4827; (iv) 88—89° (10·1 g.), $n_D^{19°}$ 1·4870; and (v) 89° (8·4 g.), $n_D^{13°}$ 1·4887. Light absorption of (v); Maximum, 2450 A.; ε, 6400. The residue remaining after the crude ketone mixture had been distilled partly solidified. Crystallisation from light petroleum (b. p. 40—60°) gave plates (1·6 g.), m. p. 47°, which were shown to consist of nonane-2 : 8-dione, probably formed from the acetylmethyl*cyclo*hexene by a reversed aldol condensation (Found: C, 69·7; H, 10·65. Calc. for $C_9H_{16}O_2$: C, 69·2; H, 10·35%). The bisdinitrophenylhydrazone had m. p. 160° (Found: C, 48·55; H, 5·1. Calc. for $C_{21}H_{24}O_8N_8$: C, 48·8; H, 4·7%) (Alder, Pascher, and Schmitz, *Ber.*, 1943, **76**, 27, give m. p. 49° for the diketone and m. p. 156° for the bisdinitrophenylhydrazone).

1-*Acetyl*-2-*methyl*cyclo*hex*-1-*ene* (I).—(*a*) The crude ketone (46·5 g.; $n_D^{20°}$ 1·478), prepared by the first method described above, on treatment with semicarbazide acetate solution in the normal manner

deposited a crystalline mass (*A*) (36 g.), m. p. 180—200°. Two recrystallisations from ethanol, followed by a recrystallisation from benzene, which did not alter the m. p., gave the semicarbazone of 1-acetyl-2-methyl*cyclo*hex-1-ene as plates, m. p. 212—214° (Ruzicka, Koolhaas, and Wind, *loc. cit.*, give m. p. 213°). Light absorption: see table.

(*b*) The crude ketone (36·5 g.; $n_D^{28°}$ 1·474), prepared by the second method described above, on treatment with semicarbazide acetate solution deposited a powder (*B*), m. p. 195—200°. Crystallisation from ethanol gave the semicarbazone of 1-acetyl-2-methyl*cyclo*hex-1-ene (23 g.) as shining plates, m. p. 213°, undepressed on admixture with the material obtained in (*a*).

The ketone was regenerated from the pure semicarbazone (22 g.) by boiling under reflux a stirred suspension in light petroleum (b. p. 60—80°) and 2N-sulphuric acid for 48 hours. This gave 1-acetyl-2-methyl*cyclo*hex-1-ene (14 g.; 90%), b. p. 98—98·5°/25 mm., $n_D^{25°}$ 1·4852. Light absorption: see table (Braude, Jones, Sondheimer, and Toogood, *loc. cit.*, for a sample obtained by the partial hydrogenation of 6-methyl-2 : 5-dihydroacetophenone, give b. p. 89—91°/14 mm., $n_D^{21°}$ 1·4842. Light absorption: Maximum, 2440 A.; ε, 6000). Alternatively, the ketone could be regenerated from the semicarbazone by steam-distillation with phthalic anhydride, whereafter the product had physical properties identical with those above. On treament with semicarbazide acetate, the pure ketone gave the semicarbazone described above [m. p. (crude) 208—214°]; it gave an oily oxime and was recovered unchanged on treatment with sodamide in ether (cf. Jones and Koch, *J.*, 1942, 393). It was similarly recovered unchanged after heating under reflux with 90% formic acid, no rearrangement to the Δ^2-isomer being observed. The 2 : 4-dinitrophenylhydrazone crystallised from ethanol in bright red plates, m. p. 125°, undepressed on admixture with the sample (m. p. 124—125°) prepared by Braude, Jones, Sondheimer, and Toogood (*loc. cit.*). Light absorption: see table.

1-*Acetyl*-2-*methyl*cyclo*hex*-2-*ene* (II).—(*a*) The mother-liquors obtained after separation of the crude semicarbazone (*A*) described above gave a solid (11 g.) on dilution with water. Repeated crystallisation from aqueous alcohol, neglecting the more insoluble fractions, followed by crystallisation from benzene, gave the *semicarbazone* of 1-acetyl-2-methyl*cyclo*hex-2-ene (5 g.) as stout prisms, m. p. 148—150° (mixed with semicarbazone of Δ^1-form, m. p. 154—190°) (Found: N, 21·7. $C_{10}H_{17}ON_3$ requires N, 21·5%). Light absorption: Maximum, 2300 A.; ε, 13,000.

(*b*) The mother-liquors obtained after separation of the crude semicarbazone (*B*) described above, gave a solid (8·9 g.) on dilution with water. Repeated crystallisation as before gave the semicarbazone of 1-acetyl-2-methyl*cyclo*hex-2-ene, m. p. 131—132° (the m. p. depends on the rate of heating and is raised to *ca.* 150° by admixture with a few % of the Δ^1-isomer. This probably explains the higher m. p. recorded above, (Found: N, 21·0. Calc. for $C_{10}H_{17}ON_3$: N, 21·5%). Light absorption: Maximum, 2270 A.; ε, 12,000.

The ketone was regenerated from the semicarbazone (4·9 g.) by steam-distillation with phthalic anhydride (10 g.) in water (100 c.c.). This yielded 1-*acetyl*-2-*methyl*cyclo*hex*-2-*ene* (2·9 g.), b. p. 83—85°/18 mm., $n_D^{20°}$ 1·4695 (Found: C, 78·1; H, 10·2. $C_9H_{14}O$ requires C, 78·3; H, 10·1%). Light absorption: ε, <600 at 2450 A. On treatment with semicarbazide acetate it gave the semicarbazone described above [m. p. (crude) 140—144°]. After treatment with sodamide in ethereal solution the ketone was recovered unchanged. When this regeneration was carried out by steam-distillation with oxalic acid instead of phthalic anhydride, complete isomerisation to the Δ^1-isomer occurred and the product had $n_D^{15°}$ 1·4891. Light absorption: Maximum, 2490 A.; ε, 6500.

In a recent paper, Dimroth and Lüderitz (*Ber.*, 1948, **81**, 242) state that the reaction of 1-methyl-*cyclo*hexene furnishes both 2-methyl-1-acetyl*cyclo*hex-1-ene and the Δ^2-isomer, but the light-absorption properties recorded for the former show that the material was not obtained pure. The m. p.s of the semicarbazones are given as 206° and 158—160°, respectively. From the rearrangement of 2-methyl-1-ethynyl*cyclo*hexanol with formic acid, Dimroth and Lüderitz report having obtained a third isomer, formulated as 1-acetyl-2-methyl*cyclo*hex-5-ene, which gives a semicarbazone, m. p. 208°. Dimroth and Lüderitz formulate the semicarbazone, m. p. 208°, as a pyrazoline derivative. This formulation is almost certainly erroneous, however, since in all analogous cases the pyrazoline derivative is obtained as a *liquid* from the semicarbazone itself, and since the derivative exhibits the expected light absorption properties (the data in the table on p. 245 appear to be transposed).

*Acetyl*cyclo*hexene*.—The ketone was prepared by methods analogous to those used for preparing the acetylmethyl*cyclo*hexene (cf., *inter al.*, Hurd and Christ, *J. Amer. Chem. Soc.*, 1937, **59**, 118; Chanley, *ibid.*, 1948, **70**, 244). The pure ketone was obtained from the semicarbazone (see below) by heating the latter under reflux with light petroleum (b. p. 60—80°) and dilute sulphuric acid. It had b. p. 90°/16 mm., $n_D^{15°}$ 1·4910. Light absorption: see table. The semicarbazone had m. p. 218—219° (Chanley, *loc. cit.*, gives m. p. 220—221°). Light absorption: see table. The 2 : 4-dinitrophenylhydrazone had m. p. 202°, undepressed on admixture with a sample (m. p. 202°) obtained by partly hydrogenating 2 : 5-dihydroacetophenone (Braude, Jones, Sondheimer, and Toogood, *loc. cit.*). Light absorption: see table. Dimroth and Lüderitz (*loc. cit.*) record light-absorption properties for the ketone and its semicarbazone almost identical with our own and also state that the semicarbazone, m. p. 210°, can be converted, by melting, into a liquid pyrazoline derivative with a maximum at 2400 A., ε, 9600.

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404. *Studies in Light Absorption. Part VII. Azines and Related Systems. A Comparison of the* –C=C– *and the* –C=N– *Chromophore.*

By H. C. Barany, E. A. Braude, and M. Pianka.

The ultra-violet light absorption of some azomethine analogues of the butadiene and diphenylbutadiene systems has been determined. The replacement of one or both ethylenic by azomethine groups results in a displacement of the maxima towards shorter wave-lengths. In polyene-azines, the hypsochromic shifts (expressed as wave-number differences) with respect to the corresponding polyene-hydrocarbons are approximately independent of the length of the polyene chain and represent an increase in the excitation energy of *ca.* 3 kcals./mol. per nitrogen atom. The spectral properties of the acyclic azomethine systems are compared with those of heterocyclic nitrogen compounds.

The effect of replacing ethylenic by azomethine groups on the ultra-violet light absorption of conjugated systems is of much interest in connection with the theory of electronic spectra. It has so far been discussed mainly in relation to cyclic systems, for which a considerable amount of experimental work is now available (cf. Bowen, *Ann. Reports*, 1943, **40**, 25; Braude, *ibid.*, 1945, **42**, 105, Maccoll, *J.*, 1946, 670). The object of the present work was to compare the –C=C– and –C=N– chromophores in linear systems of the butadiene and polyene types.

There are five possible azomethine analogues of the butadiene system, of which three, namely the enimine system –C=C–C=N–, the di-imine system –N=C–C=N–, and the azine system –C=N–N=C– are readily accessible by the condensation of appropriate carbonyl compounds and primary amines. The azomethine analogues of 1 : 4-dimethylbutadiene and 1 : 4-diphenylbutadiene have been thus prepared (see Experimental section), and their light absorption data are given in Table I and Figures 1 and 2.

The introduction of one azomethine group as in *crotonylidenebutylamine* and cinnamylideneaniline results in a slight decrease in $\lambda_{max.}$ (by 70—240 A.), whilst the introduction of two azomethine groups as in diacetyldi-*N*-butylimine and diacetylanil, and as in butyraldazine and benzylideneazine, gives rise to a somewhat larger hypsochromic shift (by 190—280 A.). The characteristic bands of most of the azomethine derivatives are slightly less intense than those of the ethylenic analogues and mostly show twin maxima, whereas only diphenylbutadiene, but not dimethylbutadiene, exhibits vibrational structure in solution. The diphenyl derivatives exhibit short-wave-length in addition to their long-wave-length absorption (Fig. 2); the former is ascribed to partial chromophores and not included in Table I. In the case of diacetyldianil, the reduction in intensity of the long-wave-length band is very pronounced, and the assignment of bands cannot be regarded as certain in this case, steric or other factors associated with the presence of the two extra methyl substituents possibly intervening. Neither glyoxaldi-*N*-butylimine nor glyoxal dianil, in which these complications would not arise, could be prepared in the pure state.

Table I.*

Replacement of –C=C– *by* –C=N– *in the butadiene and the diphenylbutadiene system.*

	$\lambda_{max.}$, A.	$\varepsilon_{max.}$		$\lambda_{max.}$, A.	$\varepsilon_{max.}$
Me·CH=CH·CH=CHMe ...	2270	22,500 [1]	Ph·CH=CH·CH=CHPh ...	3280	41,000 [2]
Me·CH=CH·CH=NBu ...	2200	23,000		3500	35,000
Bu·N=CMe·CMe=NBu ...	2060	17,000	Ph·CH=CH·CH=NPh ...	3040	30,000
	2090	18,500		3250	24,800
Pr·CH=N·N=CHPr	2050	13,000	Ph·N=CMe·CMe=NPh ...	3000	2,000
	2080	11,500		3250	2,000
			Ph·CH=N·N=CHPh	3000	36,000 [3]
				3080	35,000

* Unless otherwise stated, data in this and subsequent tables are for ethanol solutions.

[1] Booker, Evans, and Gillam, *J.*, 1940, 1453.

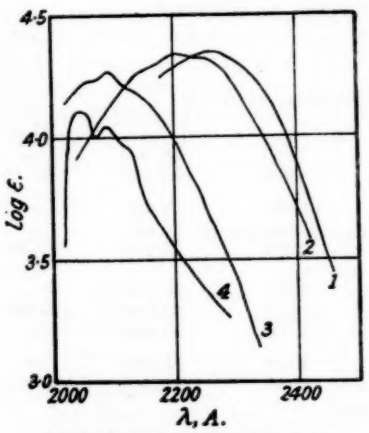
[2] Hausser, Kuhn, and Smakula, *Z. physikal. Chem.*, 1935, *B*, **29**, 384; Hausser, Kuhn, and Seitz, *ibid.*, p. 391.

[3] Ferguson and Branch, *J. Amer. Chem. Soc.*, 1944, **66**, 1467, record only one maximum at 3000 A. for this compound.

Since the effects of replacing ethylenic by azomethine groups in dimethylbutadiene and diphenylbutadiene are very similar, it was of interest to determine to what extent these effects are independent of the total length of more extended linear chromophores. This can readily be tested in the case of the azine system, where series of vinologues are known. Data for the azines of aliphatic and aromatic polyene-aldehydes, and for the corresponding polyene-hydro-

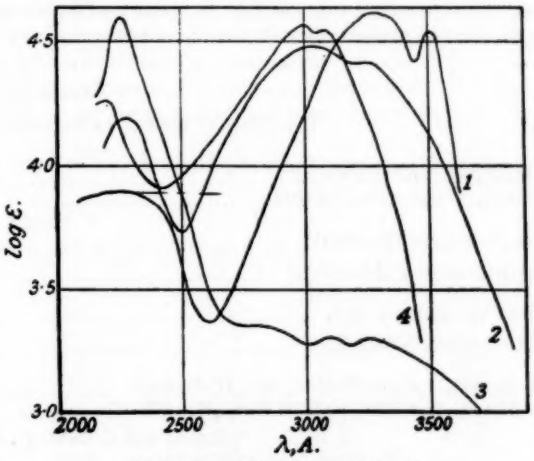
carbons, are given in Table II. The hypsochromic shift due to the azine grouping increases as the absorption maxima move towards the visible region with increasing numbers of conjugated groups, but the frequency (wave-number) differences remain reasonably constant at about 2100 cm.$^{-1}$ per azine grouping, with the exception of the first member, acetaldazine, where $\Delta(1/\lambda) = 4030$ cm.$^{-1}$ A wave-number difference of 2100 cm.$^{-1}$ represents an energy difference of 6·0 kcals./mol., or 3·0 kcals./mol. per nitrogen atom. It thus appears that the excitation energy involved in the electronic transition associated with the long-wave-length bands is increased by about 3 kcals./mol. by the replacement of an ethylenic by an azomethine group, independently of the total length of the polyene chain.

FIG. 1.



Light absorption in ethanol of
(1) Me·CH:CH·CH:CHMe,
(2) Me·CH:CH·CH:NBu,
(3) Bu·N:CMe·CMe:NBu,
(4) Pr·CH:N·N:CHPr.

FIG. 2.



Light absorption in ethanol of
(1) Ph·CH:CH·CH:CHPh,
(2) Ph·CH:CH·CH:NPh,
(3) Ph·N:CMe·CMe:NPh,
(4) Ph·CH:N·N:CHPh.

TABLE II.

Replacement of $-C{=}C-$ *by* $-C{=}N-$ *in polyene systems.*

	X = CH.		X = N.*		$\Delta(1/\lambda)$,
	$\lambda_{max.}$	$\varepsilon_{max.}$	$\lambda_{max.}$	$\varepsilon_{max.}$	cm.$^{-1}$.†
(Me·CH=X)$_2$	2270	25,000	2080	10,000	4030
(Me·CH=CH·CH=X)$_2$	2960	52,000 [1]	2770	36,000	2320
(Me·CH=CH·CH=CH·CH=X)$_2$	3600	70,000 [1]	3380	73,000	1810
(Me·CH=CH·CH=CH·CH=CH·CH=X)$_2$	4200	36,000 [1]	3850	84,000	2160
(Ph·CH=X)$_2$	3280	41,000 [2]	3040	36,000	2400
(Ph·CH=CH·CH=X)$_2$	3750	90,000 [2]	3500	65,000 [3]	2080
(Ph·CH=X·X=CH)$_2$	,,	,,	3200 ‡	42,000	2290
(Ph·CH=CH·CH=CH·CH=X)$_2$	4200	117,000 [2]	3850	48,000 [3]	2160

[1] Kuhn and Grundmann, *Ber.*, 1938, **71**, 442; Blout and Fields, *J. Amer. Chem. Soc.*, 1948, **70**, 189.
[2] Hausser, Kuhn, and Smakula, *loc. cit.*
[3] Ferguson and Branch, *loc. cit.*
* Since the completion of this work, data for the aliphatic polyene-azines, though under different solvent conditions, have been published by Blout and Fields, *loc. cit.*
† Calculated from data for dibenzylidenediacetyl dihydrazone, assuming the hypsochromic effect of the methyl groups to be similar to that in related systems (see Table III).
‡ Per azine grouping.

A striking difference in the properties of the butadiene system and its azomethine analogues is revealed by the effect of alkyl substitution (Table III). In butadiene and its derivatives, each alkyl substituent attached to the chromophoric system results in a bathochromic shift of about 50 A. (Woodward, *J. Amer. Chem. Soc.*, 1941, **63**, 1123). The effect of alkyl substituents in the enimine system can be derived by comparing the data for crotonaldehyde oxime and mesityl oxide oxime (Evans and Gillam, *J.*, 1943, 565). Crotonaldehyde oxime

exhibits a maximum at slightly longer wave-length (2295 A.) than crotonylidenebutylamine (2200 A.), in accordance with the usual greater auxochromic effect of hydroxyl as compared with alkyl substituents (cf. Part III, *J.*, 1946, 948), but there is hardly any further displacement of the maximum in mesityl oxide oxime, which has two additional methyl groups attached to the chromophoric system. A similar insensitivity to alkyl substitution is observed in other enimine derivatives, such as semicarbazones, containing the chromophoric grouping $-C{=}C{-}C{=}N{\cdot}NH{\cdot}COMe$ (Evans and Gillam, *loc. cit.*). It might perhaps be expected that the properties of the $-C{=}C{-}C{=}N-$ chromophore would be intermediate between those of the $-C{=}C{-}C{=}C-$ and $C{=}C{-}C{=}O$ chromophores. However, this is evidently not the case. Whereas the enimine analogue, crotonylidenebutylamine, absorbs maximally at a lower wave-length than dimethylbutadiene, the enone analogue, pent-3-en-2-one, absorbs at a higher wave-length ($\lambda_{max.}$ 2240 A.) and, whereas alkyl substitution is almost without effect in the enimine system, its effect in the enone is even greater than in the diene system (Evans and Gillam, *J.*, 1941, 815).

TABLE III.

The effect of methyl substituents in azomethine systems.

	$\lambda_{max.}$, A.	$\varepsilon_{max.}$	$\Delta\lambda$, A.
Me·CH=CH·CH=N·OH	2295	16,900 [1]	—
Me·CH=CMe·CMe=N·OH	2305	17,800 [1]	+ 10
HO·N=CH·CH=N·OH	2360	17,600	—
	2420	15,400	—
HO·N=CMe·CMe=N·OH	2270	18,000	−90
Ph·CH=N·N=CHPh	3000	28,000	—
Ph·CMe=N·N=CMePh	2650	20,500	−300
	2700	20,500	—
p-MeO·C_6H_4·CH=N·N=CH·C_6H_4·OMe-*p*′	3310	47,000	—
p-MeO·C_6H_4·CMe=N·N=CMe·C_6H_4·OMe-*p*′	3030	28,000	−270

[1] Evans and Gillam, *J.*, 1943, 565.

TABLE IV.

The effect of nuclear substituents in the benzylideneazine system, $C_6H_3RR'{\cdot}CH{=}N{\cdot}N{=}CH{\cdot}C_6H_3RR'$.

R.	R′.	$\lambda_{max.}$, A.	$\varepsilon_{max.}$	$+\Delta\lambda$, A.
H	H	3000, 3080	36,000, 35,000	—
o-Cl	H	3070	36,000	70
m-Cl	H	3000, 3150, 3230	38,500, 33,000, 18,000	0
p-Cl	H	3100, 3220	40,000, 36,000	100
o-OH	H	2950, 3540	30,000, 25,500	540
m-OH	H	2980, 3060, 3300	28,500, 28,000, 21,500	60
p-OH	H	3350	44,000	350
o-OH	*p*-OH	3070, 3670, 3750	12,000, 42,500, 39,000	670
o-OMe	H	2820, 2910, 3390	17,000, 18,000, 28,000	390
p-OMe	H	3300	36,000	300
m-OMe	*p*-OMe	3430	43,500	430
m-OMe	*p*-OH	3470	42,000	470
p-NMe_2	H	3220, 4000	11,000, 63,000	1000

In the di-imine system, comparing the data for glyoxime and dimethylglyoxime, the introduction of two methyl substituents actually results in a *decrease* in $\lambda_{max.}$ (by about 100 A.). An even more pronounced hypsochromic shift (by about 300 A.) occurs in the azine system, as shown by the data for benzylideneazine and phenyl methyl ketazine, and their *pp*′-dimethoxy-derivatives. Since the methyl substituents would not be expected to prevent a coplanar configuration of either the glyoxime or the benzylideneazine systems (cf. Blout, Eager, and Gofstein, *J. Amer. Chem. Soc.*, 1946, **68**, 1983), this effect is unlikely to be a steric one of the type discussed in Part VI (preceding paper), but is presumably conditioned by the electronic properties of the azomethine group.

In contrast to the somewhat unexpected hypsochromic effect of methyl substituents attached directly to the di-imine or azomethine systems, the effect of nuclear substituents in benzylideneazine is the expected bathochromic one, increasing in the order $Cl < OH < OMe < NMe_2$, as in other conjugated systems of this type (cf. Part III, *loc. cit.*) (Table IV). The displacements are least for *m*- and largest for *p*-substituents, whilst *o*-substituents often cause the splitting of the

long-wave-length bands into two subsidiary bands. This effect has already been observed and interpreted by Blout and Gofstein (*J. Amer. Chem. Soc.*, 1945, **67**, 13) with whose data our own are in reasonably good agreement as far as they overlap.

The hypsochromic effect produced by replacing ethylenic by azomethine groups may be compared with the corresponding effects observed in cyclic conjugated systems (Table V). Such a comparison can be of only limited significance since the long-wave-length bands exhibited by the cyclic systems are of low intensity and therefore due to " forbidden " transitions not analogous to those responsible for the long-wave-length absorption of the open-chain analogues (cf. Sklar, *J. Chem. Physics*, 1937, **5**, 669; Mulliken, *ibid.*, 1939, **7**, 353). However, the high-intensity bands in the 2400—2800 A. region are probably comparable, and it will be seen that, in contrast to the behaviour of open-chain systems, the introduction of a nitrogen atom produces only small and irregular changes in $\lambda_{max.}$ not exceeding 100 A. in the series pyridine, pyrimidine, and pyrazine; naphthalene, quinoline, and *iso*quinoline; and anthracene, acridine, and phenazine. The pronounced bathochromic effect observed in six-membered heterocyclic compounds containing two or more *adjacent* nitrogen atoms (*e.g.*, pyridazine, tetrazine) is probably different in origin and arises from the incursion of Kekulé structures involving $-N{=}N-$ links (cf. Maccoll, *loc. cit.*).

The theoretical interpretation of the empirical relations outlined in this paper will be discussed in a separate communication.

TABLE V.

Replacement of $-C{=}C-$ *by* $-C{=}N-$ *in cyclic systems.*

	$\lambda_{max.}$, A.	$\varepsilon_{max.}$	$\lambda_{max.}$, A.	$\varepsilon_{max.}$
Benzene	2550	250 [5]	—	—
Pyridine	2500	2,000 [5]	—	—
Pyrimidine	2430	3,000	2750	300 [2]
Pyrazine	2600	5,200	3110	580 [1]
Naphthalene	2760	7,900	3110	345 [3]
Quinoline	2750	4,500	3110	6300 [3]
*iso*Quinoline	2620	3,700	3180	3550 [3]
Anthracene	2500	160,000	3800	630 [4]
Acridine	2500	160,000	3600	1000 [4]
Phenazine	2500	120,000	3700	1600 [4]

[1] This paper.
[2] Heyroth and Loofbourow, *J. Amer. Chem. Soc.*, 1934, **56**, 1728 (in water).
[3] Morton and de Gouveia, *J.*, 1934, 911 (in hexane).
[4] Radulescu and Ostrogovich, *Ber.*, 1931, **64**, 2233.
[5] Menczel, *Z. physikal. Chem.*, 1927, **125**, 161 (in hexane).

EXPERIMENTAL.

Light-absorption Measurements.—Measurements in the region above 2200 A. were made with a Hilger medium spectrograph and Spekker photometer, as previously described (Part I, *J.*, 1945, 490). Absorption curves extending to the region below 2200 A. were determined with a Beckman DU quartz photoelectric spectrophotometer, Serial No. 1623, using 1 cm. quartz cells.

Materials.—Solids were crystallised from ethanol unless otherwise stated. Light-absorption data are given when not, or only partly, included in Tables I—V or Figures 1 and 2, and refer to solutions in ethanol unless otherwise stated. The following compounds are known. Acetaldazine (Curtius and Zinkeisen, *J. pr. Chem.*, 1898, **58**, 325), prepared by slowly adding 50% aqueous hydrazine hydrate (8 ml.) to freshly distilled acetaldehyde (11·3 ml.) at −5°, and extracting the mixture with ether, distilled as a colourless liquid, b. p. 95—96°, which very rapidly becomes yellow when kept. The light absorption is similar to that of butyraldazine (see below), but acetaldazine is very much less stable. Crotonaldazine (Hladik, *Monatsh.* 1903, **24**, 438), m. p. 98°. Sorbaldazine (Kuhn and Hoffer, *Ber.*, 1930, **63**, 2164), m. p. 170°, max. 2600 and 3380 A., ε 9200 and 73,000, respectively. Octatrienaldazine (*idem, ibid.*), m. p. 220—222° (from *n*-butanol), max. 2440, 2510, and 3850 A., ε 12,000, 12,000, and, 84,000, respectively. Benzylideneazine (Curtius and Jay, *J. pr. Chem.*, 1889, **39**, 44), m. p. 96°. 2 : 2′- (*idem, ibid.*), m. p. 214°, 3 : 3′- (Franzen and Eichler, *ibid.*, 1910, **82**, 247), m.p. 208—209°, and 4 : 4′-Dihydroxybenzylideneazine (Knopfer, *Monatsh.*, 1909, **30**, 31), m. p. 268°. 2 : 4 : 2′ : 4′-Tetrahydroxybenzylideneazine (*idem, ibid.*), m. p. 320°. 2 : 2′- (Vorlander, *Ber.*, 1906, **39**, 807), m. p. 141°, and 4 : 4-Dimethoxybenzylideneazine (Knopfer, *loc. cit.*), m. p. 170—172°. 3 : 4 : 3′ : 4′-Tetramethoxybenzylideneazine (Gattermann, *Annalen*, 1907, **357**, 668), m. p. 193—194° (from benzene). 4 : 4′-Dihydroxy-3 : 3′-dimethoxybenzylideneazine (Knopfer, *loc. cit.*), m. p. 195°. 2 : 2′- (Curtius and Pauli, *Ber.*, 1901, **34**, 849), m. p. 141°, 3 : 3′- (Curtius and Melsbach, *J. pr. Chem.*, 1910, **81**, 536), m. p. 140°, and 4 : 4′-Dichlorobenzylideneazine (Pascal and Normand, *Bull. Soc. chim.*, 1911, [iv], **9**, 1061), m. p. 208° (from benzene). 4 : 4′-Bisdimethylaminobenzylideneazine (Knopfer, *loc. cit.*), m. p. 261—262°. 2-Naphthylideneazine (Gattermann, *Annalen*, 1913, **393**, 228), m. p. 235°, max.: 2730, 2880, and 3300 A., ε 59,000, 49,500, and 69,000, respectively, inflexion

3600 A., ε 43,000. Phenyl methyl ketazine (Knopfer, *loc. cit.*), m. p. 121—122°, max.: 2650 and 2700 A., ε 20,500 and 20,500, respectively, inflexions 2780 and 2920 A., ε 19,500 and 17,000, respectively. Cinnamaldehyde anil (Doebner and Miller, *Ber.*, 1883, **16**, 1665), m. p. 109°. Diacetyldianil (Pechmann, *Ber.*, 1888, **21**, 1415), m. p. 136°. 4 : 4′-Bisdimethylamino glyoxaldianil (Pechmann and Schmitz, *Ber.*, 1898, **31**, 294), m. p. 256—257° (from xylene), maxima 2550, 3080, and 4600 A., ε 18,300, 5900, and 35,300, respectively. Dibenzylidenediacetyl dihydrazone (Darapski and Spannagel, *J. pr. Chem.*, 1915, **92**, 272), m. p. 125°, max.: 2230 and 3090 A., ε 17,000 and 42,000, respectively. Glyoxime, m. p. 179° (from water). Dimethylglyoxime, m. p. 246°. Pyrazine, m. p. 50° (distilled), kindly furnished by Professor F. S. Spring, had max.: 2560, 2600, 3110, and 3160 A., ε 4800, 5200, 580, and 560, respectively, inflexion 2660 A., ε 4000 (in ethanol), and maxima 2560, 2600, 3100, 3160, 3210, and 3270 A., ε 4550, 4700, 560, 700, 800, and 840, respectively, inflexion 2650 A., ε 3900 (in *cyclo*hexane).

The following are new:

n-*Butyraldazine*.—The azine was prepared from freshly distilled butyraldehyde, using the procedure described for acetaldazine, and distilled as a pale yellow oil, b. p. 186—188° (Found: C, 68·3; H, 11·3; N, 20·3%; *M*. in camphor, 133. $C_8H_{16}N_2$ requires C, 68·6; H, 11·4; N, 20·0%; *M*, 140). The azine has been previously prepared by Taipolie (*J. Russ. Phys. Chem. Soc.*, 1925, **57**, 506), but no details are given by this author.

Crotonylidenebutylamine.—Freshly distilled crotonaldehyde (14 g.) was added to *n*-butylamine (13·2 g.) during 30 minutes at −10° with vigorous stirring. The product was treated with an excess of solid potassium hydroxide and fractionated from fresh potassium hydroxide (cf. Tiollais, *Bull. Soc. chim.*, 1947, **14**, 708). The *imine* distilled as a pale yellow oil, b. p. 162—164°, $n_D^{23°}$ 1·4595 (Found: C, 76·5; H, 12·05; N, 11·6. $C_8H_{15}N$ requires C, 76·8; H, 12·0; N, 11·2%).

Diacetyldi-N-butylimine.—Diacetyl (7·6 g.) was added to *n*-butylamine (13·2 g.) over 1 hour at 0°. The mixture was stirred for a further 30 minutes at room temperature and then treated with an excess of anhydrous sodium sulphate. The *di-imine* distilled as a colourless liquid, b. p. 123—124°/17 mm., $n_D^{20°}$ 1·4610 (Found: C, 73·1; H, 12·1; N, 13·9. $C_{12}H_{24}N_2$ requires C, 73·5; H, 12·2; N, 14·3%). It rapidly becomes yellow on contact with air.

Benzylidenefurfurylideneazine.—A solution of furfuraldehyde (4·8 g.) and benzylidenehydrazine (6 g.) in absolute ethanol (15 ml.) was heated under reflux for 15 minutes. After the mixture had been cooled and diluted with a little water, the *azine* separated and crystallised from ethanol in needles, m. p. 63—64° (Found: C, 72·9; H, 5·2; N, 14·6%. $C_{12}H_{10}N_2$ requires C, 72·7; H, 5·1; N, 14·2%). Max. 3120 and 3240 A.; ε 3600 and 3400, respectively.

4 : 4′-*Dimethoxyphenyl Methyl Ketazine*.—The *azine* separated on adding a solution of *p*-methoxyacetophenone (7·5 g.) in ethanol (70 ml.) to a warm solution of hydrazine sulphate (3·25 g.) and sodium carbonate (2·65 g.) in water (75 ml.). It crystallised from benzene in needles, m. p. 200·5° (Found: C, 72·9; H, 6·9; N, 9·2. $C_{18}H_{20}O_2N_2$ requires C, 73·0; H, 6·8; N, 9·5%).

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405. *Studies in Light Absorption. Part VIII. Dibenzyl and Stilbene Derivatives. Interaction between Unconjugated Chromophores.*

By E. A. BRAUDE.

Existing and new spectral evidence for electronic interaction between unconjugated chromophores is reviewed. Examples of interaction in systems of the type X·CH_2·Y are provided by, *inter alia*, diphenylmethane, 1 : 4-diphenylbut-2-ene, and fluorene. Examples of interaction in systems of the type X·CH_2·CH_2·Y are provided by, *inter alia*, dibenzyl and 9 : 10-dihydrophenanthrene, and by substituted dibenzyls of the type C_6H_4R'·CHR·CHR·C_6H_4R' (R = alkyl and R′ = OH, OMe, or O·CO·Alkyl) the absorption of which differs significantly from that corresponding to a summation of the two C_6H_4R'·CHR chromophores. In substituted stilbenes of the type C_6H_4R'·CR:CR·C_6H_4R', electronic interaction between the aryl groups and the ethylenic linkage is largely inhibited by steric interference between the former and the alkyl substituents R, and the absorption is similar to that of the corresponding dibenzyls.

As a result of the interest which attaches to their œstrogenic properties, a wide range of substituted dibenzyl and stilbene derivatives has been prepared within recent years (Dodds, Lawson, Robinson, *et al.*, *Proc. Roy. Soc.*, 1939, *B*, **127**, 140; 1944, *B*, **132**, 83; for summaries see Jones, *Ann. Reports*, 1943, **40**, 137; Solmssen, *Chem. Reviews*, 1945, **37**, 481). The present work was originally undertaken in the hope that ultra-violet-light absorption might prove as valuable a criterion of chemical structure in this as in other fields. It soon became apparent, however, that the relation between structure and spectral properties in this series is one of

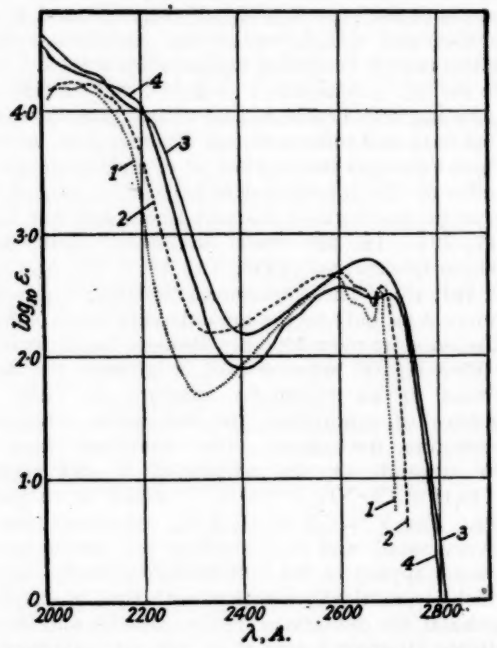
considerable complexity and presents several features of fundamental interest. The results are now presented from this latter point of view.

One of the basic principles which has long been accepted in the empirical interpretation of ultra-violet-light absorption is that the absorption due to isolated chromophores is additive, *i.e.*, that the interaction between the unsaturation electrons of groups separated by one or more saturated *carbon* atoms is too weak to affect the spectral properties. This does not, of course, apply to chromophores separated by atoms such as nitrogen, oxygen, or sulphur, which have a definite transmitting (" chromolatory ") effect ascribed to their non-bonded valency electrons (cf. Part III, *J.*, 1946, 948). The experimental evidence on which the principle of complete lack of chromolatory properties of carbon is based is not particularly extensive. Few accurate data are available for systems of the type $X\cdot[CH_2]_n\cdot Y$, where X and Y are single chromophores such as $-C{=}C-$, $-C{\equiv}C-$, $-C{=}O$ and $-CO_2H$, because the characteristic high-intensity absorption of these groups lies in the less readily accessible region below 2000 A. Among the few available examples of this type are diallyl, *cyclo*hexane-1 : 4-dione, and succinic acid which show ultra-violet absorptions corresponding very nearly to that of two propylene, acetone, and acetic acid molecules, respectively (for data and references, see Braude, *Ann. Reports*, 1945, **42**, 105). It will be noted that in all these examples the number (n) of methylene groups separating X and Y is two. Most of the studies on the interaction of isolated chromophores, however, relate to systems where X = Ph, as in the work of Ramart-Lucas and her co-workers (*Ann. Chim.*, 1931, **16**, 276; 1932, **17**, 207; **18**, 32; *Bull. Soc. chim.*, 1932, **51**, 965; 1943, **10**, 13; Grignard, " Traité de Chimie Organique," 1936, Vol. II, p. 59) and of Hillmer and Paersch (*Z. physikal. Chem.*, 1932, **161**, 46). These measurements extend only over the region of about 2300 to 3500 A. and therefore refer only to the low-intensity band (subsequently referred to as *B*-band) of the phenyl chromophore near 2600 A. Ramart-Lucas formulated the rule that, in compounds of the type $Ph\cdot[CH_2]_n\cdot Y$, when n is 2 or greater, the absorption is practically indistinguishable from that of an equimolar mixture of PhEt and EtY, but that, when n is 1, the intensities of absorption are somewhat enhanced, though the wave-length of the band remains unchanged. The deviation from additivity exhibited by derivatives $Ph\cdot CH_2\cdot Y$ depends on the nature of Y and seems to increase in the order $CN < CH{:}CH_2 < CO_2H < CO\cdot NH_2 < CO < I$, which is roughly the expected order of increasing polarisibility. For Y = CN or $CH{:}CH_2$, the deviations in the neighbourhood of the 2600 A. band are very small, and on extending the measurements on allylbenzene to 2000 A. we find that the same applies to the high-intensity band (subsequently referred to as *E* band) near 2100 A., which is practically identical with that of ethylbenzene (see fig.). For Y = CO or I, on the other hand, the deviations are considerable and the shape of the absorption curve is unmistakably altered (Ramart-Lucas *et al.*, *loc. cit.*; Hillmer and Paersch, *loc. cit.*).

Diphenylmethane and Related Systems of the Type $X\cdot CH_2\cdot Y$.—With diphenylmethane (X = Y = Ph), the absorption in the 2600 A. region exceeds only slightly that of an ethylbenzene solution of twice the molar concentration, and the deviation from additivity is only of the same order as in allylbenzene. Accurate measurements extending to 2000 A. (Ley and Specker, *Z. wiss. Photographie*, 1939, **38**, 13) show, however, that in this case there is considerable deviation from additivity in the short-wave-length region (see fig.). Not only are the intensities much increased, but a pronounced inflection, indicating a band partly submerged in the general absorption and not shown by the alkylbenzenes, appears near 2200 A. (In assessing the extent of deviations from additivity, it should be noted that, in the figure, extinction has been plotted on the usual logarithmic scale and that a difference of 0·3 in the ordinates corresponds to a two-fold change in ε.)

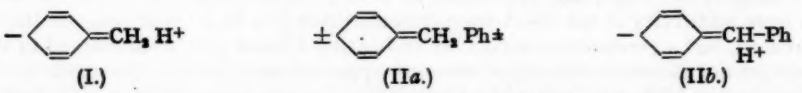
In assessing the significance of relatively small changes in absorption, two complicating factors must be borne in mind. First, absorption curves of solutions represent band envelopes in which the discrete vibrational structure has been largely obliterated by solute–solvent interaction, and the latter will be sensitive to any structural alteration in the molecule. However, the absorption of compounds of the type now considered is not very susceptible to solvent conditions (thus the data for ethanol and hexane solutions are very similar) and any solvation effects due to unconjugated substituents will therefore account only for very small deviations from additivity. Secondly, a substituent may give rise to a change in vibrational levels and hence in the shape of the band envelope of the electronic transition merely by virtue of its weighting effect. However, data for a series of alkylbenzenes (Platt and Klevens, *Chem. Reviews*, 1947, **41**, 301; *J. Chem. Physics*, 1948, **16**, 832) show that the short-wave-length (*E*) bands are almost identical throughout the series toluene to *tert.*-butylbenzene, and any vibrational effect of substituents in this region is therefore also likely to be very small. The

conclusion thus seems inescapable that the considerable deviations from additivity in the ultra-violet-light absorption of certain systems of the type $X{\cdot}CH_2{\cdot}Y$, and particularly the additional submerged band at 2200 A. exhibited by diphenylmethane are due to electronic interaction between the phenyl groups. Such interaction must take place either by way of the intervening saturated CH_2 group, or else spatially between the phenyl groups belonging to the same or different molecules. Intermolecular interaction is excluded in view of the low concentrations employed in absorption measurements and because the absorption of diphenylmethane is independent of concentration. Intramolecular spatial interaction between the two sets of π electrons also seems unlikely in view of the distance between, and the relative position of,



1. *Ethylbenzene* ($\epsilon \times 2$). 2. *Allylbenzene* ($\epsilon \times 2$).
3. *Diphenylmethane.* 4. *Dibenzyl.*

the phenyl groups. It therefore appears probable that interaction takes place by way of the intervening methylene group, a conclusion which can be expressed in terms of contributions



(I.) (II*a*.) (II*b*.)

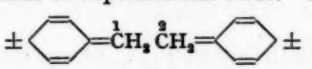
from resonance forms such as (II*a*) or (II*b*). The effect is closely akin to hyperconjugation in toluene which involves contributions from resonance forms such as (I) and also has a small, but noticeable, influence on the ultra-violet-light absorption due to the phenyl chromophore, though the *B* band alone is affected in this case (Matsen, Robertson, and Chuoke, *Chem. Reviews*, 1947, **41**, 273; Platt and Klevens, *locc. cit.*; Bowden and Braude, forthcoming paper). The same type of resonance effect is also known from chemical evidence to be operative in benzyl halides (Olivier, *Rec. Trav. chim.*, 1922, **41**, 301, 646; 1923, **42**, 516, 757; Hughes, *Trans. Faraday Soc.*, 1941, **37**, 27) and presumably occurs in benzyl derivatives CH_2PhR generally, but the fact that it is revealed also in the ultra-violet-light absorption properties does not appear to have been recognised hitherto, except in the case R = H.* From energy considerations, (II*a*) might be expected to make a greater contribution than (II*b*). However, the fact that diphenylmethane is a stronger " acid " than toluene (Conant and Wheland, *J. Amer. Chem. Soc.*, 1932, **54**, 1212) indicates that the resonance form (II*b*) plays some part. The relative importance of contributions

* Since this paper was written, the light absorption of benzyl halides has been discussed in similar terms by Hamner and Matsen, *J. Amer. Chem. Soc.*, 1948, **70**, 2482.

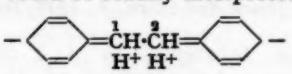
from (II*a*) and (II*b*) to the spectral effect could be tested with 2 : 2-diphenylpropane where resonance forms of the type (II*b*) are excluded, but the relevant data are not at present available.

Some further examples of the interaction of chromophores through a methylene group may be quoted. 1 : 4-Diphenylbut-2-ene exhibits a band at 2200 A., ε 13,000 (Ley and Specker, *loc. cit.*), not found in allylbenzene or toluene. The absorption of fluorene ($\lambda_{max.}$ 2600 and 3000 A., $\varepsilon_{max.}$ 19,000 and 10,000, respectively; Mayneord and Roe, *Proc. Roy. Soc.*, 1937, *A*, **158**, 634) differs significantly from that of diphenyl ($\lambda_{max.}$ 2510 A., ε 17,000). R. N. Jones (*J. Amer. Chem. Soc.*, 1941, **63**, 1658) ascribed the additional 3000 A. band in fluorene and the corresponding 2900 A. band in 9 : 10-dihydrophenanthrene (see below) to the ordinary bathochromic effect of the alkyl substituent, but this suggestion seems hardly tenable in view of the uniformly small effects of alkyl substituents in other aromatic systems. 2 : 2′-Dimethyldiphenyl cannot be used for comparison since it shows abnormal absorption occasioned by restricted rotation, but the absorptions of 3 : 3′- and 4 : 4′-dimethyldiphenyl are very similar to that of diphenyl itself and exhibit only additional *low*-intensity inflexions near 2800 A. (O'Shaughnessy and Rodebush, *J. Amer. Chem. Soc.*, 1940, **62**, 2906). Again, the absorption of *o*-xylene shows only small differences from that of toluene (Conrad-Billroth, *Z. physikal. Chem.*, 1935, **29**, *B*, 170), and the bathochromic effect of alkyl substituents at any positions in 1 : 2-benzanthracene never exceeds 50 A. (Jones, *J. Amer. Chem. Soc.*, 1940, **62**, 148). Thus, the large difference in the absorption of fluorene from that of diphenyl is almost certainly due to interaction through the methylene bridge. Such interaction is of course also indicated by the chemical properties of fluorene, particularly its high methylenic reactivity. Examples of interaction in an isocyclic system are provided by 2 : 5-dihydroacetophenones, data for which have been reported and discussed in Part V of this series (this vol., p. 607). In this case also, interaction is believed to be due largely to enhanced hyperconjugation involving the hydrogen atoms of the methylene group, as in (II*b*).

Dibenzyl and Related Systems of the Type X·CH_2·CH_2Y.—Turning now to dibenzyl, in which the two phenyl groups are separated by two methylene groups, we find that only small deviations from additivity occur with the absorption in the 2600 A. region (Ramart-Lucas, *loc. cit.*), but measurements due to Ley and Dirking (*Ber.*, 1934, **67**, 1331) and Ley and Specker (*loc. cit.*) show a new, partly submerged band (subsequently referred to as the *E′* band) near 2200 A., similar to that exhibited by diphenylmethane. A similar band is also shown by αβ-diethyldibenzyl (3 : 4-diphenylhexane) (Table I). Intramolecular spatial interaction between the π electrons of the two phenyl nuclei is even less likely in dibenzyl than in diphenylmethane in view of the steric configuration of the molecule as determined by *X*-ray analysis (Robertson, *Proc. Roy. Soc.*, 1935, *A*, **150**, 348; Jeffrey, *ibid.*, 1945, *A*, **183**, 388). The planes of the two benzene rings are inclined at an angle of 70° to the central carbon–carbon linkage and the distance between them is nowhere smaller than 4 A. There is no reason to suppose that the configuration of the molecule will be very different in solution, and electronic interaction must therefore again be taking place through the saturated carbon atoms. This is in agreement with Robertson's *X*-ray analysis which indicates a shortening of the Ph–$C_{(1)}$ and $C_{(2)}$–Ph bonds (see III) by 0·07 A. and a lengthening of the central $C_{(1)}$–$C_{(2)}$ bond by 0·04 A., although the latter difference was almost within the limits of experimental error. Such a result could be readily interpreted in terms of



(III*a*.)



(III*b*.)

small contributions from resonance forms such as (III*a*). The weakening of the central $C_{(1)}$–$C_{(2)}$ bond which it implies is of a type which would increase with the number of phenyl groups and is assumed to be partly responsible for the *ionic* dissociation of hexaphenylethane (cf. Waters, "Chemistry of Free Radicals," Oxford, 1946). The shortening of the Ph–$C_{(1)}$ and Ph–$C_{(2)}$ bonds is confirmed by the more recent analysis of Jeffrey, but, in contrast to the earlier work, a *shortening* of the central $C_{(1)}$–$C_{(2)}$ bond is indicated. In the light of the latter result, the spreading of the π electrons belonging to the phenyl groups over the central carbon chain can no longer be expressed in terms of contributions from resonance forms such as (III*a*). It could be ascribed to less likely structures such as (III*b*) analogous to (II*b*) (cf. Szwarc, Faraday Soc. Discussions, 1947, **2**, 39), but the fact that αβ-diethylbenzyl, in which the likelihood of the incursion of (III*a*)-type hyperconjugation is lessened, exhibits an *E′* band almost identical with that of dibenzyl, is against such a hypothesis.

Another interesting example of interaction through two methylene groups is provided by

9 : 10-dihydrophenanthrene. Our data for this compound agree closely with those of Jones (*loc. cit.*). In addition to a band at 2650 A. (ε 17,000) similar to that shown by diphenyl, a further band appears at 2970 A. (ε 4000) almost identical in wave-length with, but less intense than, that found in fluorene. This suggests that interaction is weaker across a $-CH_2 \cdot CH_2-$ than across a $-CH_2-$ bridge, as might be expected. A further instance of this effect occurs in bisazo-dyes of the type R·N:N·CH_2·N:N·R and R·N:N·CH_2·CH_2·N:N·R. Piper and Brode (*J. Amer. Chem. Soc.*, 1935, **57**, 135; cf. Lewis and Calvin, *Chem. Reviews*, 1939, **25**, 273) conclude that the absorptions were almost identical with those of two half-molecules R·N=N·CH_3, but the curves show considerable deviations from additivity in the short-wave-length region, with maxima near 2500 A. decreasing in intensity on passing from the methylenebisazo- to the ethane-1 : 2-bisazo- and thence to the monoazo-dye. Bateman and Koch (*J.*, 1945, 216) were unable to detect any spectral evidence for interaction in aliphatic compounds containing the system CR_2:CH·CH_2·CH_2·CH:CR_2, but *X*-ray analysis of geranylamine hydrochloride (Jeffrey, *Proc. Roy. Soc.*, 1945, *A*, **183**, 388) indicates that some interaction does occur. It has recently been shown (Barton and Cox, *J.*, 1948, 783) that optical rotation data also provide evidence for the occurrence of interaction through a chain of saturated carbon atoms, and that this effect, like the spectral one, increases with increasing polarisability of the two chromophores.

It will be clear from the above discussion that ultra-violet-light absorption evidence strongly suggests the occurrence of electronic interaction between unconjugated unsaturated groups in systems of the type X·$[CH_2]_n$·Y, when *n* is 1 or 2, though the mechanism of interaction must still be regarded as unsettled. The fact that allylbenzene exhibits very little deviation from additivity as compared with diphenylmethane, suggests that valency-bond resonance is an important factor.*

TABLE I.*

	E band.		*E′* band.		*B* band.	
	$\lambda_{max.}$, A.	$\varepsilon_{max.} \times 10^{-2}$.	$\lambda_{max.}$, A.	$\varepsilon_{max.} \times 10^{-2}$.	$\lambda_{max.}$, A.	$\varepsilon_{max.} \times 10^{-2}$.
1. Ph·CH_2·CH_2Ph (52°)	2030	300	*2190*	120	2600	3·6 [1]
2. Ph·CHEt·CHEt·Ph (88°)		†	*2180*	150	2600	3·6 [2]
3. (*p*-HO·C_6H_4·CHEt)$_2$ (188°)		†	2290	215	2800	45 [3]
4. (*p*-MeO·C_6H_4CHEt)$_2$ (142°)		†	2300	260	2770 2850	30 [4]
5. (*p*-AcO·C_6H_4·CHEt)$_2$ (125°)		†	2220	225	2560	9 [2]
For comparison :						
PhEt	2080	78	—	— ‡	2600	2·2 [2]
p-C_6H_4Me·OH	2240	68	—	—	2800	17·4 [2]
p-C_6H_4Me·OMe	2240	104	—	—	2800	22 [5]
p-C_6H_4Me·OAc	2070	81	—	—	2650	5·4 [2]

* In this and subsequent tables, figures in parentheses refer to m. p.s, and figures in italics to inflexions or " bends."

† Not determined. ‡ ε × 10^{-2} at 2190 A. = 13.

[1] Ley and Dirking, *Ber.*, 1934, **67**, 1331; Ley and Specker, *Z. Wiss. Photographie*, 1939, **38**, 13 (in methanol).

[2] This paper. [3] Elvidge, *Quart. J. Pharmacol.*, 1939, **12**, 347; 1940, **13**, 219.

[4] Kharasch and Kleimann, *J. Amer. Chem. Soc.*, 1943, **65**, 11.

[5] Braude, Jones, and Stern, *J.*, 1947, 1087.

Substituted Dibenzyls.—In 4 : 4′-dihydroxy-αβ-diethyldibenzyl (" hexœstrol ") and its dimethyl ether and diacetate (Table I), the interaction of the two benzenoid chromophores is even more pronounced than in the parent hydrocarbon, as shown by comparison of the data with those of *p*-cresol, *p*-tolyl methyl ether and *p*-tolyl acetate. In the tolyl derivatives, the *E* and

* Since this paper was written, the question of spectral interaction through a $-CH_2 \cdot CH_2-$ bridge has been examined by Koch (*J.*, 1948, 1111) in the case of dicinnamyl, CHPh:CH·CH_2·CH_2·CH:CHPh. The absorption of this compound differs significantly from that corresponding to two molecules of β-methylstyrene, and the deviations are of the same order as in the case of substituted dibenzyls, as would be expected from the above discussion. The hypothesis of electronic interaction is considered by Koch, but rejected in view of the fact that 1 : 6-distyrylhexane(1 : 10-diphenyldeca-1 : 9-diene) also exhibits some, though smaller, deviations from additivity, whereas electronic interaction through a chain of six intervening carbon atoms would be expected to be negligibly small. It seems possible that the abnormal absorption of 1 : 6-distyrylhexane is due to a steric approach of the two styryl groups situated at the overlapping ends of the coiled hydrocarbon chain. Several examples of such effects have been given by Ramart-Lucas (*loc. cit.*; cf. Fulton and Lee, *J.*, 1930, 1057). Further experimental evidence is clearly required in this field, but we consider at present that Koch's data for dicinnamyl provide definite support for the hypothesis of electronic interaction through the $-CH_2 \cdot CH_2-$ group.

B bands are displaced by *ca.* 100 and 200 A., respectively, towards longer wave-lengths relative to those shown by toluene, owing to the small bathochromic effect of the ·OR substituent. In the dibenzyls, the *E'* band is displaced still further towards longer wave-lengths by 60—100 A., and both the *E* and the *B* bands are intensified considerably beyond the expected factor of 2.

trans-*Stilbene*.—In stilbene, the saturated bridge present in dibenzyl is replaced by an ethylenic group, and the new conjugated system thus created gives rise to an intense long-wave-length band (subsequently referred to as K_3 band) near 2900 A., ascribed to the triple chromophore. In addition, stilbene exhibits shorter-wave-length bands near 2100 and 2200 A.

It is an empirical fact in ultra-violet-light absorption that a multiple chromophore usually gives rise, in addition to its own characteristic band or bands, to subsidiary bands similar to those found with the partial chromophores, and it is natural to associate the subsidiary bands with transitions involving only the unsaturation electrons of these partial structures (cf. Part I, *J.*, 1945, 490). Although the mathematical treatment of conjugated systems has not yet been carried sufficiently far to check these assignments except in a few isolated cases, there can be little doubt that they possess some fundamental significance.

In the case of stilbene, the two obvious partial chromophores are the toluene (*a*) and styrene (*b*) systems. The *E* band of the partial toluene chromophore corresponds to the 2100 A. band of stilbene, whilst the low-intensity *B* band will be masked by the intense absorption in the 2900 A. region (K_3 band).

Ph·C	Ph·C=C	Ph·C—C·Ph
(*a*)	(*b*)	(*c*)

The partial styrene chromophore appears not to be " active " since no selective absorption appears in the 2500 A. region where styrene shows its characteristic band (subsequently referred to as the K_2 band). The stilbene maximum near 2200 A. has no analogue in either the toluene or the styrene partial chromophores. It bears an obvious similarity, however, to the 2200 A. (*E'*) band exhibited by dibenzyl, and it is tentatively suggested that it is to be ascribed to the partial dibenzyl chromophore (*c*), *i.e.*, that it arises from a transition involving the unsaturation electrons of two phenyl nuclei, but not those of the intervening ethylenic link. The assumption of a partial chromophore involving non-adjacent groups is novel, and may at this stage seem somewhat implausible, but it will be shown that this assignment is strongly supported by a consideration of the data for substituted stilbenes. In terms of molecular-orbital theory, whereas the 2900 A. band in stilbene is assumed to involve the interaction of the π electrons of the two phenyl groups with the π electrons of the ethylenic link, the 2200 A. band is suggested to involve the interaction of the π electrons of the two phenyl groups with the σ electrons of the ethylenic link.

Substituted trans-*Stilbenes*.—In 4-hydroxy- and 4 : 4'-dihydroxy-*trans*-stilbenes (2, 3, Table II) the K_3 bands are displaced by *ca.* 200 A. towards longer wave-lengths as would be expected by analogy with the bathochromic effect of hydroxyl substituents in related conjugated systems (cf. styrene, 4-hydroxystyrene). The displacement of the short-wave-length band near 2200 A., on the other hand, is only small and similar to that observed on passing from dibenzyl to hexœsterol, in agreement with its designation as the *E'* band originating in the partial dibenzyl chromophore.

Introduction of an α-methyl substituent into *trans*-stilbene causes a shift of the *K* band to 2700 A., an effect which has been ascribed to steric interference between the alkyl and the (β) phenyl group, resulting in a displacement of the latter out of the plane of the ethylenic bond (Jones, *J. Amer. Chem. Soc.*, 1943, **65**, 1818). The principles underlying this effect have been discussed in Part VI of this series (this vol., p. 1890). The decrease in co-planarity will result in a decrease in the intensity of the K_3 band at 2950 A. and, at the same time, the appearance of a band near 2500 A., corresponding to the K_2 band of the remaining coplanar styrene chromophore. The very wide band around 2700 A. actually recorded is regarded as due to the superposition of the two, possibly with some true resonance degeneracy of the transitions involved. The *E'* band near 2200 A., on the other hand, is but little affected by the α-methyl substituent, again showing that it is not associated with the stilbene chromophore. Precisely similar relationships obtain in the absorption of 4 : 4'-dihydroxy-α-methylstilbene (5, Table II) as compared with 4 : 4'-dihydroxystilbene. The K_3 band near 3100 A. is replaced by a wide band near 2900 A. regarded as a combination of the reduced 3100 A. band and the 2600 A. (K_2) band expected for the partial 4-hydroxystyren chromophore. The *E'* band, on the other hand, remains unchanged and is practically identical in position with that shown by hexœstrol (Table I).

In αβ-dialkylstilbenes, steric interference occurs between both pairs of alkyl and phenyl

TABLE II.*

	E' band.		*K* band.		*B* band.	
	$\lambda_{max.}$, A.	$\varepsilon_{max.}$ × 10^{-2}.	$\lambda_{max.}$, A.	$\varepsilon_{max.}$ × 10^{-2}.	$\lambda_{max.}$, A.	$\varepsilon_{max.}$ × 10^{-2}.
1. *trans*-Ph·CH=CHPh (125°)	2260	150	2950 3100	270 [1] 250	—	—
2. *p*-HO·C_6H_4CH=CHPh (187°)	2300	175	3040 3160	235 [2] 235	—	—
3. (*p*-HO·C_6H_4·CH:)$_2$ (278°)	*2280*	125	3000 3070 3250	285 [2] 285 250	—	—
4. Ph·CMe=CHPh	*2180*	220	2700	180 [3]	—	—
5. *p*-HO·C_6H_4·CMe=CH·C_6H_4·OH-*p* (175°)	2230	115	2820 2910	270 [2] 270	—	—
6. Ph·CMe=CPhMe (107°)	2180 2400	225 120	2800 —	50 [3] —	— —	— —
7. *p*-HO·C_6H_4·CEt=CPhEt	2280	135	—	—	2790	40 [2]
8. (*p*-HO·C_6H_4·CEt:)$_2$ (171°)	2390	180	—	—	2790	70 [2]
9. (*p*-MeO·C_6H_4·CEt:)$_2$ (124°)	2400	210	—	—	2850	50 [4]
10. (*p*-AcO·C_6H_4·CEt:)$_2$ (124°)	2380	130	—	—	*2800*	10 [5]
11. (*p*-$EtCO_2$·C_6H_4·CEt:)$_2$ (107°)	2370	160	—	—	*2800*	15 [2]
For comparison.						
Ph·CH=CH_2	—	—	2440	100	2820 2920	6 [6]
Ph·CMe=CH_2	—	—	2420	100	*2820*	3 [6]
p-HO·C_6H_4·CH=CHMe	—	—	2590	185	*2890*	28 [2]
p-MeO·C_6H_4·CH=CHMe	—	—	2600	180	*2870*	33 [7]

* All the stilbene derivatives listed in this table are believed to have the *trans*-configuration.

[1] Ley and Dirking, *loc. cit.*; Ley and Specker, *loc. cit.*; cf. Solmssen, *J. Amer. Chem. Soc.*, 1943, **65**, 2370.
[2] This paper.
[3] Arends, *Ber.*, 1931, **64**, 1936.
[4] Kharasch and Kleimann, *loc. cit.*
[5] Solmssen, *loc. cit.*
[6] Ramart-Lucas and Amagat, *Bull. Soc. chim.*, 1932, **51**, 965.
[7] Hillmer and Schorning, *Z. physikal. Chem.*, 1933, **21**, *B*, 389 (in hexane).

groups and the coplanarity not only of the triple (stilbene) chromophore, but also of the remaining double (styrene) chromophore, will be largely destroyed. The main absorption appears in the short-wave-length region near 2400 A. and may be regarded as a slightly displaced *E'* band mainly due to the partial dibenzyl chromophore. As would be expected, this band is little affected by hydroxyl, alkoxyl, or acyl substituents, and the absorption of the substituted dialkylstilbenes (7—11, Table II) is very similar to that of the corresponding dibenzyls. The suggestion made by Jones (*loc. cit.*) that the 2400 A. band in αβ-dimethylstilbene is to be ascribed to the partial styrene chromophore is difficult to reconcile with steric considerations and would appear to be excluded by the insensitivity of the band to substituent effects, which is in contrast to the displacement of the K_3 band at 2470 A. in styrene to 2600 A. in 4-hydroxystyrene and anethole. The substituted stilbenes also exhibit absorption in the 2800 A. region, of considerably higher intensity than the *B* bands shown by the corresponding *p*-tolyl and hexœstrol derivatives. This may be due either to increased dibenzyl-type interaction of the aryl groups, or to the retention of a small degree of triple chromophore character, or both.

cis-*Stilbene Derivatives.*—*cis*-Stilbene (Table III) exhibits bands near 2200 and 2800 A., analogous to the *E'* and K_3 bands of stilbene. The decreases in $\lambda_{max.}$ and $\varepsilon_{max.}$ of the K_3 band as compared with those of the *trans*-isomer are to be ascribed, respectively, to the shorter length of the conjugated system in the *cis*-configuration and to the decrease in coplanarity owing to steric interference between the *o*-hydrogen atoms of the phenyl groups. In the diacetate and dipropionate (2, 3, Table III), believed to be derivatives of the unknown *cis*-stilbœstrol, the intensity of the K_3 band is still further reduced. In this case, scale models indicate that steric interference will occur between the ethyl and phenyl groups attached to the *same* carbon atom, whereas in the *trans*-derivatives interference is between alkyl and phenyl groups attached to different carbon atoms. The interpretation to be given to the submerged bands near 2500 A. also exhibited by the presumed *cis*-stilbœstrol derivatives, however, is not clear.

ψ-Stilbœstrol and Dienœstrol.—Data for a number of miscellaneous dibenzyl and stilbene derivatives are collected in Table IV. ψ-Stilbœstrol (1) and its diacetate (2), which may be regarded either as substituted dibenzyls or as α-benzylstyrenes, show only dibenzyl-type (*E'*) bands in the 2300 A. region, but no styrene-type absorption, in agreement with

their expected non-planar configuration. In dienœstrol (3) and its acetate (4), which may be regarded either as substituted dibenzyls or as 1 : 2-diphenylbutadienes, the 2300 A. band is much enhanced in intensity and is probably a superposition of absorption due to the partial butadiene and dibenzyl chromophores. The isomeric *iso*dienœstrol (5), on the other hand, shows styrene type absorption corresponding almost exactly to the summation of two enol (4-hydroxy-β-methylstyrene) systems. In this compound, the two halves of the molecule appear to be separately coplanar, and a model can be constructed in which this is the case, and in which the two planes containing the enol systems are at approximately right angles to each other.

TABLE III.

	E' band.		*K* band.	
	$\lambda_{max.}$, A.	$\varepsilon_{max.} \times 10^{-3}$.	$\lambda_{max.}$, A.	$\varepsilon_{max.} \times 10^{-3}$.
1. *cis*-Ph·CH=CH·Ph	2220	230	2800	135 [1]
2. (*p*-AcO·C_6H_4·CEt:)$_2$ (82°) *	2230	145	*2560*	100 [2]
			2780	70
3. (*p*-$EtCO_2$·C_6H_4CEt:)$_2$ (78°) *	2280	135	2500	105 [2]
			2800	80

* Believed to have the *cis*-configuration.

[1] Ley and Dirking, *loc. cit.* [2] This paper.

TABLE IV.

	E' band.		*K* band.		*B* band.	
	$\lambda_{max.}$, A.	$\varepsilon_{max.} \times 10^{-3}$.	$\lambda_{max.}$, A.	$\varepsilon_{max.} \times 10^{-3}$.	$\lambda_{max.}$, A.	$\varepsilon_{max.} \times 10^{-3}$.
1. *p*-HO·C_6H_4(:CHMe)·CHEt·C_6H_4·OH-*p* (151°)	2290	185	—	—	2800	40 [1]
2. *p*-AcO·C_6H_4·C(:CHMe)·CHEt·C_6H_4·OAc-*p* (64°)	2230	185 [1]	—	—	—	—
3. *p*-HO·C_6H_4·C(:CHMe)·C(:CHMe)·C_6H_4·OH-*p* (230°)	2290	275	—	—	2800	95 [1]
4. *p*-AcO·C_6H_4·C(:CHMe)·C(:CHMe)·C_6H_4·OAc-*p*	2250	260	—	—	*2800*	15 [1]
(115°)	2450	145				
5. *iso*Dienœstrol (189°)	—	—	2590	285	*2950*	50 [1]

[1] This paper.

EXPERIMENTAL.

For the technique of light-absorption measurements, see Parts I (*J.*, 1944, 490) and VII (preceding paper). Data are for ethanolic solutions unless otherwise stated. All the compounds examined are described in the literature, except the diacetate and dipropionate 2 and 3 (Table III), which were very kindly furnished by Dr. E. Walton before publication. Many of the other samples were obtained through the courtesy of Professor E. C. Dodds, F.R.S., Professor E. E. Turner, F.R.S., Dr. W. C. J. Ross and Dr. F. N. Short. Ozonolysis of dienœstrol diacetate (4, Table IV) (1 g.) in acetic acid (50 ml.) for 20 hours (200 mg. of O_3 per hour) and decomposition of the ozonide by the method of Church, Whitmore, and McGrew (*J. Amer. Chem. Soc.*, 1934, **56**, 176) afforded 200 mg. (15%) of the dimedone derivative of acetaldehyde, m. p. 139°, undepressed by an authentic specimen.

The author thanks Professor Sir Ian Heilbron, D.S.O., F.R.S., for his interest, and Professor E. R. H. Jones, at whose suggestion this work was originally undertaken, for helpful criticism.

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406. *Keto–Enol Equilibria of Ethyl Acetoacetate in Solution. Dielectric Polarisation Indications.*

By R. J. W. LE FÈVRE and H. WELSH.

The dielectric polarisations of equilibrated ethyl acetoacetate in a number of solvents have been measured at 25°. From the squares of the apparent moments so obtained the following enol-percentages at infinite dilution are calculated : in hexane, 63; in carbon tetrachloride, 25; in benzene, 25; in carbon disulphide, 43; in toluene, 39; in ether, 14; in chloroform, *ca.* 0. These figures are reconcilable with recorded analyses by Meyer's bromine-titration method. No correlations with specific properties of the media have been discovered.

THIS paper concerns the effects of media on the keto–enol equilibrium of ethyl acetoacetate, for which nearly all the recorded data have hitherto been obtained by the " bromine titration "

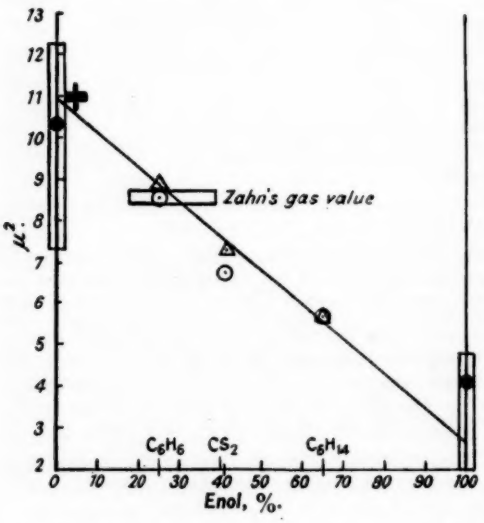
procedure of Meyer and his collaborators (*Annalen*, 1911, **380**, 226; *Ber.*, 1911, **44**, 2718; 1912, **45**, 2852; *Ber.*, 1920, **63**, 1410). Conant and Thompson (*J. Amer. Chem. Soc.*, 1932, **54**, 4039) later used Meyer's original form in estimating the free energy change of enolisation, notwithstanding criticisms and modifications of this technique previously made by Grossmann (*Z. physikal. Chem.*, 1924, **109**, 305) and Hantzsch and Krober (*ibid.*, 1930, **147**, 293). It is well known that consistency of numerical results can be obtained only by an exact adherence to a set manipulative routine. It seemed, therefore, that check analyses by different means might be useful. Physical methods (in which the tautomeric components are not subjected to reagents) are obviously preferable. To date—with the single exception of refractometry—these have not been accurately applied to solutions (see Beilstein, "Handbuch, Erste Ergänzungs-Werk," III, 223, for summary and references).

Present Work.—We have accordingly investigated the suitability of dielectric-polarisation measurements for this purpose. The apparent dipole moments of ethyl acetoacetate have been determined in seven solvents by routine methods (see Experimental section for details). Our values are listed in Table I:

TABLE I.

Solvent:	Hexane.	C_6H_6.	CS_2.	CCl_4.	PhMe.	$CHCl_3$.	Et_2O.
$_\infty P_1$ (at 25°), c.c.	151	209	173	228	192	263	155
$\mu_{apparent}$, D.	2·39	2·92	2·60	3·07	2·75	3·36	2·42

These data of course refer to the ester at "infinite dilution," a condition which enables the effects of different solvents to be expressed on an equivalent basis. Such results, however, cannot immediately be compared with those by "bromine titration." Fortunately Meyer and Kappelmeier tabulate analyses in benzene, hexane, and carbon disulphide, over wide concentration ranges [at room temperature, it is true, but for the pure liquid "das Gleichgewicht verändert sich bis zum Siedepunkt kaum mit der Temperatur" (Beilstein, *loc. cit.*), whilst for solutions, the changes for a 5° interval are small—probably not more than 2% of the enol content (Meyer and Willson, *Ber.*, 1914, **47**, 832)]. We find that their figures plot smoothly against proportions of total solute in the solutions, and at $w_1 = 0$ indicate an enol-% of 65 in *n*-hexane, 25 in benzene, and 41 in carbon disulphide. If it is accepted that at equilibrium our solutions can be regarded as containing only two forms, of unknown moments μ_E and μ_K respectively, then the squares of these moments should be related to $\mu^2_{apparent}$ by a simple-mixture formula.



As a first check we explored this possibility by plotting observed μ^2 values against the enol-percentages quoted above (see figure, points ⊙). The three points *suggest* that a straight line relation may not be incorrect. The present measurements are almost certainly not free from "solvent" influences. By noting the moments found by Müller (*Physikal. Z.*, 1933, **34**, 5) for acetone in these solvents, and adjusting (by simple proportion) our observations to "gas" values (using the *squares* of the moments since it is the orientation polarisation, a function of μ^2, which varies with the solvent) we obtained results lying nearer to a straight line (figure, points Δ compared with points ⊙).

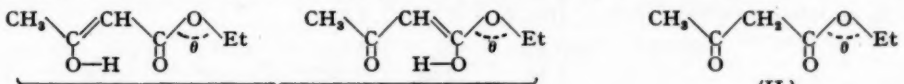
A further datum can be obtained from the liquid equilibrium ester, from which enol contents of from 2% (by refractive index measurements; Knorr, Rothe, and Averbeck, *Ber.*, 1911, **44**, 1147) to 7·4% (by bromine titration; Meyer, *loc. cit.*) are recorded. In another connection, Onsager (*J. Amer. Chem. Soc.*, 1936, **58**, 1486) has shown that the true orientation polarisation of a molecule should be expressible by terms including the dielectric constant, density, and refractive index, as measured for the *liquid* (and not the dissolved or gaseous) phase, by:

$$_0P = \frac{(\varepsilon - n^2)(2\varepsilon + n^2)}{\varepsilon(n^2 + 2)^2} \cdot \frac{M}{D}$$

whilst Böttcher (*Physica*, **1939**, **6**, 59) has tested this calculation successfully for eighteen substances, *including* acetone and ethyl acetate. It may therefore apply to ethyl acetoacetate. We have accordingly made the necessary determinations at 25° (see Experimental section), and find ${}_0P = 224{\cdot}5$ c.c., from which a theoretical μ_{gas} value (corresponding to 2—7% of enol) of 3·3 D. is obtained. The appropriate indication on the figure is +.

Only one direct measurement of the moment of vapourised ethyl acetoacetate is available (Zahn, *Physikal. Z.*, 1933, **34**, 570). Observations were made over the rather small temperature interval 394—431° K. The apparent moment lay between 2·91 and 2·95 D. (average quoted by Zahn, 2·93 D). The keto–enol proportions present under Zahn's conditions are unknown, but the reasonable guess may be made (bearing in mind the experimental procedure commonly adopted for estimating the dielectric constants of relatively high-boiling liquids) that the equilibrium approximated to that occurring in the vapour entering the condenser during a normal vacuum distillation. Knorr, Rothe, and Averbeck (*loc. cit.*) have examined such condensates, finding enol-percentages ranging from 18 to 39%. The area bounded by these extremes and $\mu^2 = 8{\cdot}47$—$8{\cdot}70$ is included on the figure.

Numerical Values of μ_E and μ_K.—The limits within which these are likely to fall can be estimated if (*a*) the configurations of both forms are such that the heavier component atoms in each are as nearly as possible in common positions, (*b*) the O · · · · H · · · · O bridge is rectilinear, between 2·4 and 2·8 A. in length (Robertson, *Trans. Faraday Soc.*, 1940, **36**, 913), and has no resultant moment towards either oxygen atom, and (*c*) the carbethoxy-group retains throughout the " *trans* "-structure assigned to it by Marsden and Sutton (*J.*, 1936, 1383).



(I.) (II.)

Accordingly we consider, as the major contributing forms, (I) and (II), where all carbon-intervalency angles are approximately 120°, whilst θ (cf. Bennett, *Trans. Faraday Soc.*, 1934, **30**, 853; Hampson, Farmer, and Sutton, *Proc. Roy. Soc.*, 1933, **143**, *A*, 158) may vary from 60° (as in ethylene oxide, $\mu_{gas} = 1{\cdot}9$ D.) to 110—120° (as in diethyl ether, $\mu_{gas} = 1{\cdot}1$ D.; see *Trans. Faraday Soc.*, 1934, appendix, for all values of μ quoted without reference).

The chief polar links will produce resultants, for (I), of 1·0 + 2·3 − (1·1 to 1·9) = 2·2 to 1·4 D., and, for (II), of 2 × 2·3 − (1·1 to 1·9) = 3·5 to 2·7 D. (Eucken and Meyer's link moments, *Physikal. Z.*, 1929, **30**, 397, being used, and the fragment Me—C$\langle$O being taken as equivalent to a component of 1 D. acting along the C—O bond). These ranges are indicated on the two ordinates of the figure. Beyaert (*Natuurw. Tijdschr.*, 1937, **19**, 197) has recorded an attempt at direct measurement on the enolic form at −80° in carbon disulphide solution. The moment found was 2·04 D. Using this figure and assuming that the ester was 16·8% enolised in benzene, he estimated μ_{keto} from observations at room temperatures in this solvent as 3·22 D. (see figure, points ●). Beyaert notes that during solubility experiments at −80° in carbon disulphide no correction was made for the small amount of the ketonic form present, and we therefore suspect that his value of μ_{enol} is thereby too high, and, consequently, his μ_{keto} too low. This is consistent with the figure (which suggests $\mu_{keto}/\mu_{enol} = 3{\cdot}3/1{\cdot}7$).

Relative Proportions at Equilibrium.—From the figure the approximate proportions in each solvent at infinite dilution appear to be as in Table II.

TABLE II.

Solvent.*	% enol.	Enol/keto ratio.
Hexane	63	1·70
Carbon tetrachloride	25	0·33
Carbon disulphide	43	0·75
Benzene	25	0·33
Toluene	39	0·64
Ether	14	0·16

* Listed in ascending order of $\varepsilon_{25°}$.

The case with chloroform as a solvent has not been included since it may be exceptional. It is known that chloroform–acetone mixtures show abnormalities in several physical properties, notably vapour pressure, viscosity, dielectric polarisation, and infra-red spectrum. For the third of these, Glasstone (*Trans. Faraday Soc.*, 1937, **33**, 200) found unexpectedly high values,

attributed to association of a co-operative type ($R_2C\overrightarrow{=}O\ H\overrightarrow{-}CCl_3$, where the arrows indicate the directions of the contributing moments, to which must be added induced moments acting in the same sense). As to the infra-red spectra, Gordy (*J. Chem. Physics*, **1939**, **7**, 163) observed that neither of these two liquids alone had an absorption band near 4μ, which was however displayed prominently by mixtures. He interpreted this as evidence of an intermolecular H bond ($Cl_3C—H—O{=}CMe_2$). Such suspicions are further justified by the work of Horiuti and Sakamoto (*Bull. Chem. Soc., Japan*, **1936**, **11**, 627) which demonstrates (by the ready exchange between hydrogen and deuterium in heavy water) that the H of $CHCl_3$ has a tendency to separate as a proton in certain circumstances.

Similar factors may operate with ethyl acetoacetate in chloroform. Meyer (*loc. cit.*) reports about 92% of the keto-form in such solutions. The qualitative indications of our measurements are likewise that the enol-percentage is extremely small.

General Solvent Effects on Equilibrium.—As a preliminary it is relevant to mention that recorded investigations (Beilstein, *op. cit.* for references) have shown ethyl acetoacetate to be unimolecular in solution.

Like many previous authors (Michæl and Hibbert, *Ber.*, 1908, **41**, 1080; Dimroth, *Annalen*, 1910, **377**, 127; Meyer, *ibid.*, 1911, **380**, 226) we have explored the possibility of a general quantitative correlation between enol : keto ratios and single properties of solvents. From Table II it is obvious that the numerical value, alone, of the dielectric constant (cf. *Annalen*, 1913, **399**, 91) is not immediately connected with either the enol-percentage or the enol/keto ratio. Some signs of parallelism have been found with expressions of the type : Enol-% $= 100 \cdot e^{-\mu_{enol}(\varepsilon-1)/\mu_{keto}} = 100 \cdot e^{-1\cdot7(\varepsilon-1)/3\cdot3}$, *e.g.* :

Solvent :	Hexane.	CS_2.	PhMe.	C_6H_6.	CCl_4.	Et_2O.
ε	1·89	2·63	2·37	2·27	2·23	4·27
Obs. Enol-%	63	43	39	25	25	14
Calc. ditto	63	44	49	52	53	19

Similar attempts, introducing other intuitively reasonable physical data, have not been more successful. Whenever ε is involved, *trends* in accord with experiment are forecast, *e.g.*, that solvents with large dielectric constants should give low enol-percentages. The case when $\varepsilon = 1$ (*i.e.*, the gaseous state) should correspond to an enol-percentage of 100. This, on thermodynamic grounds, could never be wholly correct, but no protracted equilibrations in the vapour state are yet on record (the work of Zahn, and Conant *et al.* involved the near participation of the *liquid* phase).

Earlier discussions on reciprocal reactions (*e.g.*, by van't Hoff, " Lectures on Theoretical and Physical Chemistry," trans. Lehfeldt, Arnold, 1898, **1**, 221) do not greatly assist the setting up of " models " for keto–enol–solvent systems. The " van't Hoff–Dimroth rule " has, of course, been found applicable to an assorted range of equilibria (Moelwyn-Hughes, " Kinetics of Reactions in Solution," 2nd Edn., Oxford Univ. Press, 1947, 188), but it utilises solubility data which themselves are of an experimental nature and not yet related to specific molecular quantities. We feel that the stabilisation of the keto-form through H-bonding with another molecule (*e.g.*, $R{\cdot}O—H\cdots O{=}CMe{\cdot}CH_2{\cdot}CO_2Et$), may be one important part of a qualitative explanation of solvent effects. To this we would add the extra stability which surrounding polar solvent molecules could confer on (II) by association with antiparallel alignment of dipole moments. Thus, solvents which readily form H-bonds with ketones or which possess high localised polarities (localised because certain mutual geometrical requirements are obvious) should show preferential development of the keto-form. That such a prediction is broadly in agreement with facts is seen, not only from our own results at infinite dilution, but also from those of Meyer *et al.* (*loc. cit.*, although these refer to various concentrations, and might be different at infinite dilution) :

Solvent :	H_2O.	$H{\cdot}CO_2H$.	AcOH.	MeOH.	EtOH.	Pure ester.	$COMe_2$.	$PhNO_2$.
Temperature, °c. ...	0	20	20	0	0	20	0	18
%-Enol	0·4	1·1	5·7	6·9	12·7	7·4	7·3	10·1

In neutral solvents of low polarity (*e.g.*, hydrocarbons, which do not normally engage in H-bonding) the ester is free to form its internal H-bridge. It evidently does this more easily than the related intermolecular process. Were this not so, the liquid equilibrium (pure ethyl acetoacetate) would be *ca.* 50 : 50 and not 7 : 93 as actually observed. Noting, however, that Badger and Bauer (*J. Chem. Physics*, **1936**, **4**, 469, 71; **1937**, **5**, 839) have found diacetone alcohol—whose structure should favour internal chelation—to have less than 0·75 of its molecules

chelated in carbon tetrachloride solution, we infer that the factors leading to an internal H-bond can sometimes only slightly outweigh those leading to an external one. In the condensed phase of ethyl acetoacetate, therefore, association by dipole–dipole forces may control the equilibrium; the fact that dissolution in acetone (similar μ and ε values) does not significantly alter the enol-%, further supports this.

We conclude, accordingly, that the predominant determinant of the keto–enol ratio lies with the keto- and not the enol-form. Of course, strongly basic (Brönsted sense) solvents might assist enolisation *via* intermolecular association (*e.g.*, $C_5H_5N \cdots H—O—CMe{=}CH{\cdot}CO_2Et$) but experimental studies in such media are, at present, sparse.

Experimental.

Materials.—The solvents used were prepared for use as follows. Hexane, by shaking with sulphuric acid, washing, drying (Na), distillation, and storage over sodium wire; benzene, by drying "thiophen-free" material (Na wire), partly freezing, decanting, and storing the remelted portion over sodium wire; carbon tetrachloride, by boiling under reflux over mercury, shaking with sulphuric acid, dilute aqueous sodium hydroxide, and water successively, drying ($CaCl_2$), fractionating, and storing over calcium chloride; carbon disulphide, by prolonged shaking of an "AnalaR" sample with mercury and calcium chloride, fractionating, and storing in dry air; chloroform, by shaking with aqueous sodium hydrogen sulphite, water, concentrated sulphuric acid, and water, followed by fractionating, and storing over calcium chloride; ether, by shaking with aqueous silver nitrate, dilute aqueous sodium hydroxide, and water, drying ($CaCl_2$, before Na wire), fractionating, and storing over sodium; toluene, by shaking with concentrated sulphuric acid, then dilute aqueous sodium hydroxide, then water, drying ($CaCl_2$, then Na), distilling, and storing over sodium wire.

Ethyl acetoacetate, as purchased (B.D.H.), was dried ($CaCl_2$ or Na_2SO_4), filtered, and distilled. Only the middle third, b. p. 89°/30 mm. (cf. 87·8°/29·32 mm., Beilstein, Handbuch, *loc. cit.*), was collected. Solutions were prepared by weight and set aside overnight at room temperature before any measurements were made; this precaution seemed desirable in view of the reports concerning time variance of the initial densities, viscosities, and magnetic susceptibilities of freshly distilled batches of ester (cf. Beilstein, *op. cit.*, p. 224). The measurements of Grossmann (*loc. cit.*) on the rates of enolisation of the keto-form, however, indicate that equilibrium is established in ordinary glass containers in less than 12 hours.

Apparatus.—Preliminary observations (by G. J. Rayner, made at University College, London, 1939), which are incorporated in Table I, were obtained with the resonance apparatus described in "Dipole Moments" (Methuen, London, 1938, p. 29). For the majority of the data, however, the simpler circuits mentioned recently (Calderbank and Le Fèvre, *J.*, 1948, 1949; *op. cit.*, 2nd Edn., 1948, Chapter II) have been utilised.

The pure ester was examined in a small (about 5-c.c. capacity) Pyrex cell, the plates of which were constructed from two 1·5-cm. lengths of brass tubing, spaced with glass beads, and supported by stout tungsten wires passing through the glass to mercury-containing side-arms. From the latter, connection was made directly to a co-axial union, mounted on the bridge holding the cell assembly in the thermostat, and from thence, *via* 2 feet of co-axial cable, to the oscillator chassis. The cell was filled and emptied by suction without removal.

Readings on the variable condenser were noted with air and a number of reference liquids filling the cell. Together with the solvents listed below, we have used purified ethylene dichloride and acetone, standard figures for which are available:

$C_2H_4Cl_2$: $\varepsilon_{25°} = 10{\cdot}35_8$ (Davies, *Phil. Mag.*, 1936, **21**, 1008).
$\varepsilon_{25°} = 10{\cdot}36 \pm 0{\cdot}02$ (Sugden, *J.*, 1933, 768).
C_3H_6O: $\varepsilon_{25°} = 19{\cdot}11_5$, from $\log \varepsilon = 1{\cdot}2914 - 0{\cdot}00201$ ($t° - 20°$), Åkerlof (*J. Amer. Chem. Soc.*, 1932, **54**, 4125).
$\varepsilon_{25°} = 19{\cdot}06$ (Le Fèvre, *Trans. Faraday Soc.*, 1938, **34**, 1127).

A mean value of (Reading plus liquid minus reading plus air)/($\varepsilon - 1$) was so obtained. Ethyl acetoacetate, which had stood for 2 days in a glass flask after distillation, was then drawn into the cell, etc., its dielectric constant at 25° being thus determined as 15·33 (average result of 5 experiments; Drude, *Z. physikal. Chem.*, 1897, **23**, 267, gives 15·7 at 22°). For the application of Onsager's equation (see above) we have calculated n^2 from $[R_L]_D = 32{\cdot}1$ and $d_4^{25} = 1{\cdot}022$ (Dunstan and Stubbs, *J.*, 1908, **93**, 1921).

Solutions.—Data for these are tabulated below under: w_1, the weight fractions of ester in the solutions; ε, the dielectric constants of the latter; and d, their densities. Subscripts 1 and 2 refer to solute and solvent respectively. The quantity $a\varepsilon_2$ represents $(\varepsilon_{12} - \varepsilon_2)/w_1$, which is required later (p. 1914).

The dielectric constants of all solutions are relative to the appropriate pure solvents, for which values have been taken, as follows:

Solvent:	$\varepsilon^{25°}$.	Source.
Hexane	1·8938	Determined against benzene.
Benzene	2·2725	Hartshorne and Oliver, *Proc. Roy. Soc.*, 1929, **123**, 664.
Carbon disulphide	2·6349	Determined against benzene.
Carbon tetrachloride	2·2270	Le Fèvre, *loc. cit.*
Toluene	2·3666	Determined against benzene.
Chloroform	4·7240	Ball, *J.*, 1930, 570.
Ether	4·265	Le Fèvre, *loc. cit.*

Hexane.

$100w_1$.	ε_{12}^{25}.	d_4^{25}.	$100w_1$.	ε_{12}^{25}.	d_4^{25}.
0	1·8938	0·65542	9·425	2·2820	0·67626
1·737	1·9554	0·65906	12·235	2·4223	0·68293
2·671	1·9874	0·66107	14·275	2·5335	0·68768
5·614	2·1107	0·66751	17·577	2·7319	0·69614
5·706	2·1124	0·66770	19·269	2·8411	0·70038
5·725	2·1195	3·66799	21·008	2·9594	0·70473
6·013	2·1303	0·66863			

Benzene.

0	2·2725	0·87378	6·423	2·7585	0·88153
0·6216	2·3162	0·87457	7·101	2·8098	0·88236
1·229	2·3580	0·87529	7·843	2·8674	0·88354
1·732	2·3942	0·87587	9·140	2·9578	0·88533
1·9245	2·4060	0·87615	11·745	3·2070	0·88855
2·150	2·4308	0·87669	12·144	3·2419	0·88909
3·264	2·5072	0·87770	18·101	3·8102	0·89692
3·873	2·5480	0·87852	21·233	4·1294	0·90104
4·2575	2·5788	0·87867	24·827	4·5167	0·90593
4·604	2·6163	0·88001	31·157	5·2347	0·91470
4·632	2·6230	0·87937			

Carbon disulphide.

0	2·6349	1·2585	6·914	3·2968	1·2324
0·8536	2·7045	1·2551	8·461	3·4600	1·2269
2·853	2·8927	1·2473	10·067	3·6386	1·2214
2·976	2·9023	2·2469	14·115	4·1134	1·2080
5·160	3·1171	1·2387			

Carbon tetrachloride.

0	2·2270	1·5844	3·4168	2·6303	1·5544
1·0082	2·3612	—	4·4055	2·7008	1·5480
1·8346	2·4559	1·5687	5·1067	·27871	1·5386
2·7389	2·5623	—	5·3960	2·8390	1·5356
3·0524	2·5983	1·5570	10·246	—	1·4899

Toluene.

0	2·3666	0·86051	8·3270	2·9588	0·87058
1·1248	2·4392	0·86183	11·058	3·1043	0·88010
3·6517	2·6093	0·86452	15·922	3·6155	0·88024
4·1189	2·6288	0·86573	20·542	4·0048	0·88592
5·2530	2·7318	0·86663			

Chloroform.

0	4·7240	1·4678	4·2566	5·9833	1·4405
2·3513	5·4318	1·4526	4·5524	6·0355	1·4387
3·0942	5·6523	1·4478	6·7401	6·5496	1·4255
3·2911	5·7080	1·4466	7·1733	6·6861	1·4230

Ether.

0	4·265	0·70768	6·1221	4·679	0·72204
1·4401	4·348	0·71040	6·2188	4·691	0·72224
1·8484	4·378	0·71047	9·3786	4·910	0·72919
2·1948	4·405	0·71195	9·8144	4·940	0·73104
3·3755	4·474	0·71558	10·584	5·009	0·73343
5·7518	4·652	0·72180	11·135	5·050	0·73490

Inspection will reveal that in most cases $\alpha\varepsilon_2$ and βd_2 are not invariant with w_1. Since the ratio keto/enol changes with concentration this is not unexpected. The dependence is, however, rectilinear. We have accordingly calculated ${}_\infty P_1$ (the total polarisation at infinite dilution) from the values of $\alpha\varepsilon_2$ and βd_2 extrapolated to $w_1 = 0$, the equation, ${}_\infty P_1 = M_1[p_2(1 - \beta) + C\alpha\varepsilon_2]$, being used (cf. *J.*, 1937, 1805). The molecular refraction is taken as 33 c.c. from several data recorded in the literature (cf. Beilstein, *op. cit.*).

Calculations of apparent moments, etc.

Solvent.	$(\alpha\varepsilon_2)_{w_1=0}$.	$(\beta d_2)_{w_1=0}$.	c.	p_2.	${}_\infty P_1$.	$\mu_{app.}$, D.
Hexane	3·40	0·207	0·3019	0·3502	151	$2·3_9$
Ether	5·06	0·090	0·1080	0·7364	155	$2·4_2$
Carbon disulphide	8·67	0·398	0·1180	0·2803	173	$2·6_9$
Toluene	6·36	0·115	0·1828	0·3637	192	$2·7_5$
Benzene	7·00	0·121	0·1881	0·3409	209	$2·9_3$
Carbon tetrachloride	13·90	−0·853	0·1060	0·1832	228	$3·0_7$
Chloroform	32·65	−0·665	0·4521	0·3773	263	$3·3_6$

We are indebted to the Commonwealth Science Fund for a Senior Studentship to one of us (H. W.) and to this Society for the continued rétention of apparatus originally provided by a grant from its Research Committee.

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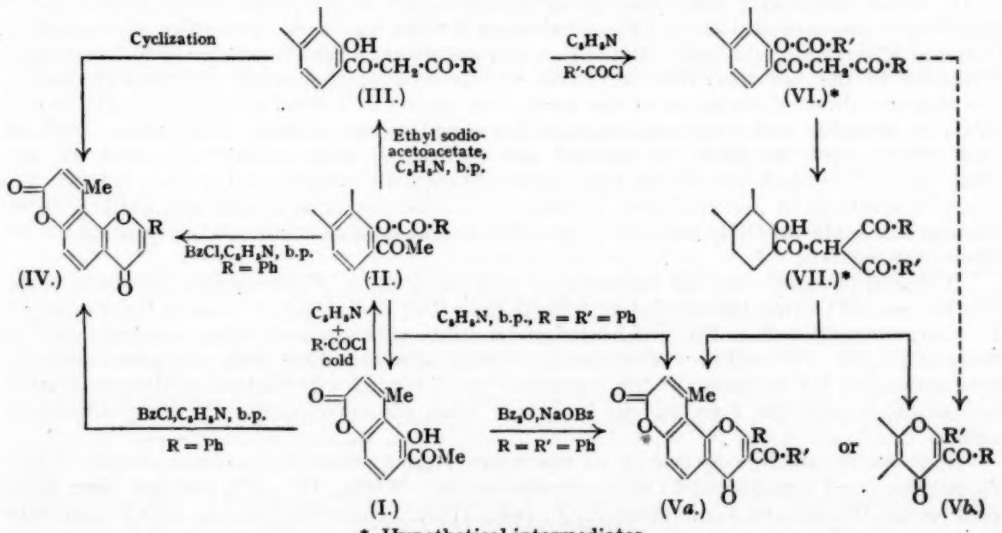
407. *The Action of Benzoyl Chloride and Pyridine on 5-Hydroxy-6-acetyl-4-methylcoumarin and Reactions related thereto.*

By G. J. BERNFELD and T. S. WHEELER.

5-Hydroxy-6-acetyl-4-methylcoumarin (I) with benzoyl chloride and pyridine in the cold gives the 5-benzoate (II; R = Ph) which can be transformed into the 5-hydroxy-diketone (III; R = Ph) by an intramolecular Claisen condensation. Both these products can be cyclized to 2′-phenyl-4-methylchromono(7′ : 8′-6 : 5)pyr-2-one (IV; R = Ph), previously (Shah and Deliwala, *Proc. Indian Acad. Sci.*, 1942, **16**, 387) obtained by the direct action of benzoyl chloride in *boiling* pyridine on (I). The 5-hydroxy-diketone is probably not an intermediate, as postulated by Shah and Deliwala, in this direct formation of (IV) from (I), since benzoyl chloride and pyridine introduce a further benzoyl group to yield 3′-benzoyl-2′-phenyl-4-methylchromono(7′ : 8′-6 : 5)pyr-2-one (V; R = R′ = Ph). This 3′-benzoyl derivative is also formed by the action of pyridine alone on a mixture of the 5-benzoate (II) and 5-hydroxy-diketone (III).

Several analogous reactions are effected with other aroyl chlorides.

SHAH AND DELIWALA (*Proc. Indian Acad. Sci.*, 1942, **16**, 387) found that, when 5-hydroxy-6-acetyl-4-methylcoumarin (I) was heated with benzoyl chloride and pyridine, there resulted, not the expected benzoyl derivative (II; R = Ph), but the flavone, 2′-phenyl-4-methylchromono(7′ : 8′-6 : 5)pyr-2-one (IV; R = Ph). These authors suggested that the reaction proceeds through the ester (II; R = Ph) and the hydroxy-diketone (III; R = Ph) with subsequent cyclization to (IV; R = Ph). The transformation of *o*-aroyloxyacetoarones into *o*-hydroxydibenzoylmethanes, involved in the step (II) ⟶ (III), was first effected by Baker



* Hypothetical intermediates.

(*J.*, 1933, 1381) using potassium carbonate, and independently by Venkataraman and his collaborators (*Current Sci.*, 1933, **2**, 214; *J.*, 1934, 1767) using sodamide. It has been shown by Wheeler and his colleagues (Ullal and Wheeler, *Current Sci.*, 1938, **7**, 280; Wheeler, *Chem. and Ind.*, 1947, 753; Doyle *et al.*, *Proc. Roy. Dublin Soc.*, 1948, **24**, 291) that this transformation involves a base-catalysed intramolecular Claisen condensation between an ester and a methyl ketone, a wide variety of bases (alkali-metal salts of weak acids, *e.g.*, ethyl sodioacetoacetate) being effective.

The suggestion of Shah and Deliwala in regard to the course of their reaction is supported

by the fact that (I) with benzoyl chloride and pyridine under mild conditions gives the expected ester, *5-benzoyloxy-6-acetyl-4-methylcoumarin* (II; R = Ph), which with ethyl sodioacetoacetate in pyridine yields by transformation the diketone *5-hydroxy-6-benzoylacetyl-4-methylcoumarin* (III; R = Ph). The last compound is rapidly cyclized to (IV; R = Ph), *e.g.*, by hydrogen bromide in acetic acid, by anhydrous pyridine, or by a mixture of pyridine and pyridine hydrochloride such as would be formed in the benzoylation of (I) with benzoyl chloride and pyridine. Analogous *esters* (II; R = *o*-tolyl or *p*-nitrophenyl) and *diketones* (III; R = *o*-tolyl or *p*-nitrophenyl) were similarly prepared. Compound (III; R = *o*-tolyl) was cyclized to the *flavone* (IV; R = *o*-tolyl). Further, (II; R = Ph) gives (IV; R = Ph) when heated with pyridine and an excess of benzoyl chloride, the yield (30%) being better than that (a trace) obtained when (I) is used as starting substance. It may be noted that no definite compound resulted when (I) was heated with *o*-toluoyl or *p*-nitrobenzoyl chloride and pyridine.

Action of Pyridine and Aroyl Chlorides on the Diketone (III).—Although supported by the experiments just described, Shah and Deliwala's mechanism is inadequate to explain the fact that the diketone (III; R = Ph), benzoyl chloride, and pyridine, when heated at the boiling point, give a good yield of 3′-benzoyl-2′-phenyl-4-methylchromono(7′ : 8′-6 : 5)pyr-2-one (V; R = R′ = Ph), previously synthesised by Sethna, Shah, and Shah (*J.*, 1938, 228) by aroylation of (I) with sodium benzoate and benzoic anhydride. A similar result is obtained with (III; R = *o*-tolyl) and *o*-toluoyl chloride. These observations show that (III; R = Ph) is an unlikely intermediate in Shah and Deliwala's reaction; it is more probable that (II; R = Ph), on formation from (I) by the action of benzoyl chloride and pyridine, gives (IV; R = Ph) by dehydration. Slavin (M. Sc. Thesis, University College, Dublin, 1948) found that 5-benzoyloxy-6-acetylindane is cyclized to 6-phenylindano(5′ : 6′-2 : 3)pyr-4-one by heating in glycerol.*

In the presence of pyridine (III; R = Ph) with *o*-toluoyl chloride, and (III; R = *o*-tolyl) with benzoyl chloride, give the same aroylflavone, either (V*a*) or (V*b*), and a single product is similarly obtained by both methods in the *p*-nitrophenyl series. These results are best interpreted by assuming that reaction proceeds through the ester (VI) and its transformation compound, the triketone (VII). Interchange of R and R′ in (VI) will give the same compound (VII), which presumably will cyclize in one direction only, to give either (V*a*) or (V*b*). On the other hand, direct cyclization of (VI) as indicated (broken line) would give different compounds, if R and R′ were interchanged. Baker (*loc. cit.*) postulated a similar intermediate formation of triketone in the salt–anhydride acylation of *o*-hydroxyacetophenones to 3-acylchromones. He regarded direct *C*-acylation of the methylene carbon of a diketone such as (III) to form (VII) as probable under the conditions of his experiments. Claisen *et al.* (*Ber.*, 1900, **33**, 1242, 3778; 1903, **36**, 3674; cf. Michael and Carlson, *J. Amer. Chem. Soc.*, 1935, **57**, 165; 1936, **58**, 353) found however that ethyl acetoacetate with pyridine and an acyl chloride give *O*-acyl derivatives of the enol form, so that direct *C*-benzoylation is, perhaps, unlikely in the passage from (III) to (VII) induced by pyridine and an acyl chloride; (VI) is perhaps a more likely intermediate.

It should be noted that the formation of only one form of (V) eliminates the possibility of the flavone (IV) being intermediately formed from (III) and then aroylated in the 3′-position. Further, when (IV; R = Ph) was heated under reflux with benzoyl chloride and pyridine, no trace of (V; R = R′ = Ph) was obtained. Wittig (*Annalen*, 1926, **446**, 155) also found that chromones are not acylated in the 3-position when heated with sodium acetate and acetic anhydride, though the 3-acylflavone is formed when the corresponding hydroxy-diketone is used.

Removal by alkaline hydrolysis of the 3′-aroyl group from (V), as with simpler 3-acylchromones (*e.g.*, 3-propionyl-2 : 6-dimethylchromone; Wittig, *loc. cit.*), has not been found possible (cf. Bhullar and Venkataraman, *J.*, 1931, 1165). Hence the formula of (V) is uncertain in that it may be either (V*a*) or (V*b*). This, however, does not invalidate the argument as to the course of the reaction, which requires only that different products should not be formed. Work is in progress to elucidate the structure of (V).

Action of Pyridine on the Ester (II).—While investigating the mechanism of the production of (IV; R = Ph) from (I) by the action of benzoyl chloride and pyridine, we heated the ester

* (Added 20th April 1949.) This assumption of direct cyclization is now supported by the fact that (II; R = Ph) yields (IV; R = Ph) when heated in glycerol at 220° in a current of coal gas. This method provides a simple synthesis of flavones, details of which will be published later. It is of interest to note that Chada and Venkataraman (*J.*, 1933, 1074) found that 1-benzoyloxy-2-acetonaphthone did not cyclize under the influence of dehydrating reagents.

(II; R = Ph) with pyridine alone to determine if transformation to (III) occurred. Unexpectedly a mixture of (V; R = R′ = Ph) and (I) was obtained. The *o*-toluoyl ester (II; R = *o*-tolyl) gave a similar result. It would appear that pyridine, acting as a base, transforms part of (II) into (III) and that the aroyl group in the unchanged part of (II) wanders to the methylene carbon of (III) to give the phenol (I) and the triketone (VII), which then cyclizes to (V) :

$$(II) \xrightarrow{C_5H_5N} (III) + (II) \xrightarrow{C_5H_5N} (VII) + (I) \xrightarrow{-H_2O} (V) + (I)$$

The second reaction, formation of (VII) + (I), may be regarded as involving a Claisen condensation between the diketone (III) and the ester (II), (I) being the alcohol (phenol) eliminated. The reaction mechanism is supported by the fact that heating 1 g. each of (II; R = Ph) and (III; R = Ph) with pyridine gives 0·7 g. each of (I) and (V; R = R′ = Ph); and a similar result was obtained with the *o*-tolyl derivatives.

The intermediate formation of the triketone (VII) is indicated by similar results. Compound (II; R = *o*-tolyl) with (III; R = Ph) in hot pyridine gives one form of (V; R = Ph; R′ = *o*-tolyl) and (I). The same form of (V) was similarly obtained from (II; R = Ph) and (III; R = *o*-tolyl). Further, this compound (V) was identical with that formed, as already mentioned, from (III; R = Ph) and *o*-toluoyl chloride, and from (III; R = *o*-tolyl) and benzoyl chloride.

It should be noted that the ester (II) is particularly reactive since (III; R = Ph) in the presence of pyridine gave no definite product with phenyl benzoate or *o*-benzoyloxyacetophenone. Pyridine as a solvent appears to be essential since fusion of an equimolecular mixture of (II; R = Ph) and (III; R = Ph) at 220° for 2 hours gave back (III; R = Ph) unchanged.

Experimental.

Esters of Hydroxycoumarins.—*5-Benzoyloxy-6-acetyl-4-methylcoumarin* (II; R = Ph) (5·2 g.) separated when a mixture of 5-hydroxy-6-acetyl-4-methylcoumarin (I) (5 g.) (Sethna, Shah, and Shah, *J.*, 1938, 228), benzoyl chloride (4 g.), and pyridine (25 ml.) which had been kept for 24 hours was poured into excess of dilute hydrochloric acid at 0°; crystallised from alcohol, it melted at 120—121°. (Found : C, 70·7; H, 4·6. $C_{18}H_{14}O_5$ requires C, 70·8; H, 4·3%).

5-o-Toluoyloxy- (II; R = *o*-tolyl) (from ligroin), m. p. 126—127° (Found : C, 71·5; H, 5·0. $C_{20}H_{16}O_5$ requires C, 71·4; H, 4·8%), and *5-p-nitrobenzoyloxy-6-acetyl-4-methylcoumarin* (II; R = *p*-nitrophenyl) (from alcohol and glacial acetic acid), m. p. 159—160° (Found : C, 62·2; H, 3·6; N, 3·9. $C_{18}H_{13}O_7N$ requires C, 62·1; H, 3·5; N, 3·8%), were prepared in similar yields from (I) and *o*-toluoyl and *p*-nitrobenzoyl chloride, respectively.

The esters formed needles.

o-Hydroxydiketones.—*5-Hydroxy-6-benzoylacetyl-4-methylcoumarin* (III; R = Ph) (4·5 g.) (from dioxan), m. p. 240°, separated when a mixture of (II; R = Ph) (5 g.), ethyl sodioacetoacetate (5 g.), and pyridine (25 ml.), which had been heated under reflux for 20 minutes and kept at room temperature for 12 hours, was poured into excess of 10% hydrochloric acid containing ice (Found : C, 70·4; H, 4·5. $C_{18}H_{14}O_5$ requires C, 70·8; H, 4·3%).

5-Hydroxy-6-o-toluoylacetyl-4-methylcoumarin (III; R = *o*-tolyl) (from chloroform and alcohol), m. p. 176—177° (Found : C, 70·7; H, 4·9. $C_{20}H_{16}O_5$ requires C, 71·4; H, 4·8%), and *5-hydroxy-6-p-nitrobenzoylacetyl-4-methylcoumarin* (III; R = *p*-nitrophenyl), m. p. 300° (decomp.) (from nitrobenzene) (Found : C, 62·0; H, 3·7; N, 3·5. $C_{18}H_{13}O_7N$ requires C, 62·1; H, 3·5; N, 3·8%), were similarly prepared from (II; R = *o*-tolyl) and (II; R = *p*-nitrophenyl), respectively.

These diketones were obtained as yellow needles, yields being almost quantitative.

Chromonopyr-2-ones.—2′-Phenyl-4-methylchromono(7′ : 8′-6 : 5)pyr-2-one (IV; R = Ph) (from dioxan), m. p. 263—264°, separated in almost quantitative yield, when a solution of (III; R = Ph) in acetic acid containing 50% hydrogen bromide was diluted with water. Cyclization of (III; R = Ph) to (IV; R = Ph) was also effected by boiling with anhydrous pyridine for 4 hours with or without addition of concentrated hydrochloric acid (0·1 vol.). Compound (IV; R = Ph) (0·3 g.) also separated when a mixture of (II; R = Ph) (1 g.), benzoyl chloride (2 g.), and pyridine (2 ml.) was heated under reflux for 4 hours and then poured into excess of 10% hydrochloric acid containing ice. (Added 20.4.1949). This flavone was also prepared by heating (II; R = Ph) with glycerol (10 parts) for 4 hours at 220° in a current of coal gas; the reaction mixture was poured into water, and the yellow precipitate (yield 40%) was recrystallised several times from dioxan. The m. p. of each specimen of (IV; R = Ph) was not depressed by the addition of an authentic sample prepared from (I) by the action of benzoyl chloride and pyridine (Shah and Deliwala, *Proc. Indian Acad. Sci.*, 1942, **16**, 387) (Found : C, 74·7; H, 3·9. Calc. for $C_{18}H_{12}O_4$: C, 75·0; H, 3·9%).

2′-o-Tolyl-4-methylchromono(7′ : 8′-6 : 5)pyr-2-one (IV; R = *o*-tolyl) (from dioxan), m. p. 310°, separated in needles in almost quantitative yield when (III; R = *o*-tolyl) was kept in acetic acid containing 50% hydrogen bromide for 24 hours, and then diluted with water (Found : C, 74·8; H, 4·5. $C_{20}H_{14}O_4$ requires C, 75·5; H, 4·4%).

No useful result was obtained by heating (III; R = Ph) with benzoyl chloride under reflux for 4 hours.

Aroyl Derivatives of Chromonopyr-2-ones.—(a) *Action of pyridine and aroyl chlorides on* (III). The diketone (III) was heated under reflux with the aroyl chloride (one part) and pyridine (15—20 parts)

for 4 hours, and the product (*ca.* 80% yield) separated by pouring the mixture into excess of 10% hydrochloric acid containing ice.

3′-Benzoyl-2′-phenyl-4-methylchromono(7′ : 8′-6 : 5)pyr-2-one (V; R = R′ = Ph), prepared from (III; R = Ph) and benzoyl chloride, crystallised from glacial acetic acid, had m. p. 304—306°, not depressed by addition of an authentic specimen prepared by salt–anhydride aroylation of (I) (Sethna, Shah, and Shah, *loc. cit.*) (Found : C, 76·0; H, 3·9. Calc. for $C_{25}H_{16}O_5$: C, 76·5; H, 3·9%).

3′-o-*Toluoyl*-2′-o-*tolyl*-4-*methylchromono*(7′ : 8′-6 : 5)*pyr*-2-*one* (V; R = R′ = *o*-tolyl) (from tetrahydrofurfuryl alcohol), m. p. 334—335° was prepared from (III; R = *o*-tolyl) and *o*-toluoyl chloride (Found: C, 75·9, 76·1, 75·8, 75·6, 76·1; H, 4·7, 4·7, 4·8, 4·6, 5·0. $C_{28}H_{20}O_5$ requires C, 77·0; H, 4·6; $C_{28}H_{20}O_5,0{\cdot}5H_2O$ requires C, 75·5; H, 4·7%). Flavones frequently retain water, even when heated in a high vacuum (cf. Robinson and Venkataraman, *J.*, 1929, 61; Shah, Metha, and Wheeler, *J.*, 1938, 1555). Attempts to determine combined water were unsuccessful, owing to sublimation, which occurred in a high vacuum (*ca.* 10^{-4} mm.) at the requisite temperature (220°).

3′-*Benzoyl*-2′-o-*tolyl*- or 3′-o-*toluoyl*-2′-*phenyl*-4-*methylchromono*(7′ : 8′-6 : 5)*pyr*-2-*one* (V*a* or V*b*; R = *o*-tolyl; R′ = Ph) (from chloroform–alcohol), m. p. 310—312° (Found : C, 76·3; H, 4·5. $C_{31}H_{18}O_5$ requires C, 76·7; H, 4·3%), was prepared from (III; R = Ph) and *o*-toluoyl chloride, and from (III; R = *o*-tolyl) and benzoyl chloride.

3′-*Benzoyl*-2′-p-*nitrophenyl*- or 3′-p-*nitrobenzoyl*-2′-*phenyl*-4-*methylchromono*(7′ : 8′-6 : 5)*pyr*-2-*one* (V*a* or V*b*; R = *p*-nitrophenyl; R′ = Ph) (from aqueous acetone), m. p. 310° (decomp.) (Found : C, 68·3; H, 3·3; N, 3·2. $C_{31}H_{15}O_7N$ requires C, 68·9; H, 3·3; N, 3·1%), was prepared from (III; R = Ph) and *p*-nitrobenzoyl chloride, and from (III; R = *p*-nitrophenyl) and benzoyl chloride.

These compounds formed needles.

(b) *Action of pyridine on* (II; R = Ph or *o*-tolyl). A solution of (II; R = Ph) (2 g.) in pyridine (20 ml.) was heated under reflux for 4 hours, poured into an excess of 10% sodium hydroxide solution, and filtered. The precipitate (0·15 g.), crystallised from glacial acetic acid, had m. p. 304—306°, not depressed by admixture with an authentic sample of (V; R = R′ = Ph) prepared according to Sethna, Shah, and Shah (*loc. cit.*). Acidification of the filtrate gave (I) (1·3 g.), the identity of which was confirmed by mixed m. p. after recrystallisation. When (II; R = *o*-tolyl) was used, the product (V; R = R′ = *o*-tolyl) was identical (mixed m. p.) with a sample obtained from (III; R = *o*-tolyl) and *o*-toluoyl chloride as described above.

(c) *Action of pyridine and esters of* (I) *on* (III). 1 G. each of (II; R = Ph) and (III; R = Ph), when treated as in (*b*), gave (mixed m. p.) 0·7 g. each of (V; R = R′ = Ph) and (I). Similarly a mixture of (II; R = *o*-tolyl) and (III; R = *o*-tolyl) gave (V; R = R′ = *o*-tolyl) and (I).

Compound (V*a*) or (V*b*) (R = *o*-tolyl; R′ = Ph), m. p. 310—312° not depressed by admixture with the product from (*a*) above, was obtained, together with (I), by heating for 4 hours with pyridine under reflux equimolecular mixtures of (II; R = *o*-tolyl) and (III; R = Ph) or of (II; R = Ph) and (III; R = *o*-tolyl). The products were formed in 70% yield and were worked up by the method described in (*b*).

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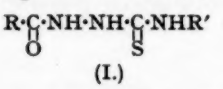
408. *Compounds Related to Thiosemicarbazide. Part III.* 1-*Benzoyl*-S-*methylisothiosemicarbazides.*

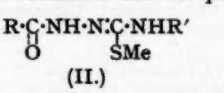
By ERIC HOGGARTH.

1-Benzoylthiosemicarbazides form *S*-methyl derivatives which readily cyclise with loss of methanethiol to give 2-amino-5-phenyl-1 : 3 : 4-oxadiazoles. The 1-benzoyl-*S*-methyl*iso*-thiosemicarbazides have been subjected to treatment with acids and bases under conditions similar to those used with the parent compounds (Part II), and the constitution of the products has been established.

1-BENZOYLTHIOSEMICARBAZIDES (Part II, this vol., p. 1163) (I; R = Ph or *p*-MeO·C_6H_4, R′ = H) in alcoholic solution reacted with methyl iodide to give the hydriodides of the corresponding 1-*benzoyl*-S-*methyl*iso*thiosemicarbazides* (II). The free *S*-methyl*iso*thiosemicarbazides were more conveniently prepared in N-sodium hydroxide, and with this variation the *compounds* (II;



(I.)

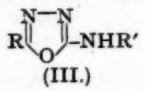


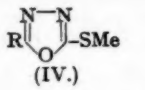
(II.)

R = *p*-NO_2·C_6H_4 or *p*-C_6H_4Cl, R′ = H), (II; R = Ph, R′ = Me, Pr^i, or Ph), and (II; R = *p*-MeO·C_6H_4, R′ = Me) as well as the foregoing, were prepared. These *S*-methyl derivatives were crystalline solids whose melting points, determined in the usual way (with slow heating), were in some cases higher than those of the parent compounds. The reason for this unusual behaviour is that on heating, methanethiol is readily lost with formation of 2-amino-5-

phenyl-1 : 3 : 4-oxadiazoles (III). If the *S*-methyl compounds are placed in a hot bath they melt with vigorous effervescence and resolidify. An analogous ready elimination of methanethiol has been described by Arndt and Tscherscher (*Ber.*, 1923, **56**, 1984) for the *S*-methyl ether of phenylguanylthiosemicarbazide, NHPh·C(:NH)·NH·NH·C(SMe):NH. For comparison, 2-amino-5-phenyl-1 : 3 : 4-oxadiazole (III; R = Ph, R′ = H) was prepared as described by Fehrenbach and Stollé (*J. pr. Chem.*, 1929, **122**, 289), and their method was extended to the preparation of the *compounds* (III; R = *p*-MeO·C_6H_4 or *p*-C_6H_4Cl, R′ = H).

The cyclisation reactions of 1-benzoyl-*S*-methyl*iso*thiosemicarbazides, like those of the parent 1-benzoylthiosemicarbazides (Part II), are greatly influenced by the nature of the agent used. The ease with which methanethiol is lost, however, is usually reflected in the isolation of appreciable amounts of the corresponding amino-oxadiazole. When heated with syrupy phosphoric acid (preferably with the addition of some phosphoric oxide) the compounds (II; R = Ph, *p*-MeO·C_6H_4, or *p*-C_6H_4Cl, R′ = H) gave, in addition to the amino-oxadiazoles (III), the corresponding benzoic acids and a third type of substance which was insoluble in both acids and alkalis. The best yields of the neutral compounds were obtained at rather lower temperatures than used in the initial experiments, and as a rule some unchanged *S*-methyl*iso*thiosemicarbazides


(III.)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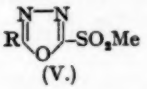
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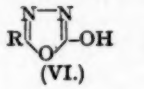
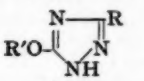
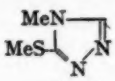

(VI.)


(VII.)


(VIII.)

were then isolated in place of the amino-oxadiazoles. Increasing the reaction time gave tarry products. Unlike the 1-benzoylthiosemicarbazides which are dehydrated by phosphoric or sulphuric acid to give the same products, the compound (II; R = Ph, R′ = H) gave only benzoic acid with 95% sulphuric acid. The neutral compounds have been shown to be *2-methylthio-5-phenyl*-1 : 3 : 4-*oxadiazoles* (IV; R = Ph, *p*-MeO·C_6H_4 or *p*-C_6H_4Cl), and this unexpected elimination of the nitrogen atom was confirmed by showing that the three compounds (II; R = Ph, R′ = H, Me, or Pr^i) gave the same neutral compound (IV; R = Ph), and both (II; R = *p*-MeO·C_6H_4, R′ = H or Me) gave (IV; R = *p*-MeO·C_6H_4).

The cyclisation of *S*-methyl*iso*thiosemicarbazides having a terminal methyl group was complicated by the occurrence of another new compound. In the case of (II; R = Ph, R′ = Me) the acid-soluble fraction has been shown to be a mixture of two compounds with very similar properties. These are *2-methylamino-5-phenyl*-1 : 3 : 4-*oxadiazole* (III; R = Ph, R′ = Me) and *5-methylthio-3-phenyl-4-methyl*-4 : 1 : 2-*triazole* (VIII). The constitution of the latter was settled by comparison with the product of the methylation of the parent thiol (Part II). In the case of (II; R = Ph, R′ = Pr^i) unchanged starting material (only) was found in the acid-soluble fraction. Further proof of the constitution of the methylthio-oxadiazoles has been found in their oxidation to sulphones (V; R = Ph, *p*-MeO·C_6H_4, or *p*-C_6H_4Cl). The oxidation of the first two examples (with permanganate) was normal, but the *p*-chloro-compound gave also appreciable amounts of *p*-chlorobenzoic acid. The sulphones have labile methanesulphonyl groups. They dissolve in cold N-sodium hydroxide, giving salts of *2-hydroxy-5-phenyl*-1 : 3 : 4-*oxadiazoles* (VI; R = Ph, *p*-MeO·C_6H_4, or *p*-C_6H_4Cl) and react readily with amines. Compound (V; R = Ph) with *iso*propylamine gave the *amino-oxadiazole* (III; R = Ph, R′ = Pr^i) which confirms the assigned structures. Reaction with 2-diethylaminoethylamine took place (exothermically) at 70—80°, and the following *compounds* were prepared: (III; R = Ph, *p*-MeO·C_6H_4, or *p*-C_6H_4Cl, R′ = $[CH_2]_2$·NEt_2).

On heating with sodium ethoxide solution, 1-benzoyl-*S*-methyl*iso*thiosemicarbazides gave, in addition to the amino-oxadiazoles, *5-ethoxy-3-phenyl*-1 : 2 : 4-*triazoles* (VII; R = Ph, *p*-MeO·C_6H_4, or *p*-C_6H_4Cl, R′ = Et). The constitution of the ethers (VII) was established by acid hydrolysis to 5-hydroxy-3-phenyl-1 : 2 : 4-triazoles (VII; R = Ph, *p*-MeO·C_6H_4, or *p*-C_6H_4Cl, R′ = H). Young and Witham (*J.*, 1900, **77**, 226) prepared (VII; R = Ph, R′ = H) by oxidation of benzaldehyde semicarbazone with ferric chloride. This and the two other *hydroxy-triazoles* were prepared by this alternative route for comparison, and it has been shown that considerable quantities of the corresponding azines (not noted by Young and Witham) are formed as by-products. The by-products of this reaction were examined to ascertain whether or not 2-amino-5-phenyl-1 : 3 : 4-oxadiazoles were also formed in analogy with the oxidation of benzaldehyde thiosemicarbazones to aminothiadiazoles. No acid soluble material was found. The use of sodium methoxide in place of the ethoxide with (II; R = *p*-MeO·C_6H_4, R′ = H) gave the *methoxy-triazole* (VII; R = *p*-MeO·C_6H_4, R′ = Me) which was hydrolysed to the same hydroxy-triazole as was the corresponding ethoxytriazole.

Comparison of the behaviour of the *S*-methyl ethers of 1-benzoylthiosemicarbazides with that of the parent compounds is complicated by the ready formation of 2-amino-oxadiazoles by the former. However, both give triazole derivatives with sodium alkoxide solutions, and the formation of oxadiazole derivatives from the ethers under acid conditions corresponds to the formation of 2-amino-5-phenyl-1 : 3 : 4-thiadiazoles by the parent compounds. Breakdown to the benzoic acids, noted in the parent series only with the *p*-methoxybenzoyl compounds, is more generally encountered with the ethers.

Experimental.

After initial experiments, all crystallisations of *S*-methyl*iso*thiosemicarbazides were made by adding the vacuum-dried crude product to hot solvent, filtering rapidly, and chilling the filtrate slightly before leaving it to crystallise. This is necessary to avoid loss of methanethiol, especially in the case of 1-benzoyl-4-phenyl-*S*-methyl*iso*thiosemicarbazide.

1-*Benzoyl*-S-*methyliso*thiosemicarbazide (II; R = Ph, R′ = H).—(*a*) 1-Benzoylthiosemicarbazide (6·5 g.) in alcohol (250 c.c.) at 60° was shaken in a stoppered bottle with a solution of methyl iodide (5·5 g.) in alcohol (30 c.c.) and set aside for 12 hours. The hydriodide obtained by evaporation under reduced pressure was dissolved in water (250 c.c.), filtered (charcoal), and made just alkaline with sodium carbonate. The solid (6·5 g.) was collected and crystallised from ethyl acetate (containing a little alcohol), giving the *product* as large highly-refractive prisms or needles (3·9 g.), m. p. 233° (decomp.) (melting with vigorous effervescence and resolidification in a bath at 180°) (Found: C, 51·5; H, 5·3; N, 19·8; S, 15·8. $C_9H_{11}ON_3S$ requires C, 51·7; H, 5·3; N, 20·1; S, 15·3%).

(*b*) 1-Benzoylthiosemicarbazide (9·8 g.) in N-sodium hydroxide (50 c.c.) was shaken for 20 minutes with methyl iodide (3·5 c.c.) in alcohol (10 c.c.), and the solid collected and crystallised as above, giving stout refractive needles (7·8 g.), m. p. 233—234° (decomp.).

1-p-*Methoxybenzoyl*-S-*methyliso*thiosemicarbazide (II; R = *p*-MeO·C_6H_4, R′ = H).—(*a*) 1-*p*-Methoxybenzoylthiosemicarbazide (11·0 g.) in 2-ethoxyethanol (700 c.c.) at 50° reacted with methyl iodide (7·8 g.) in alcohol (50 c.c.) to give the S-*methyliso*thiosemicarbazide (10·0 g.), which crystallised from methyl alcohol in colourless needles (5·0 g.), m. p. 244° (decomp.) (melts with effervescence and resolidification in a bath at 200°) (Found: C, 50·5; H, 5·6. $C_{10}H_{13}O_2N_3S$ requires C, 50·2; H, 5·4%).

(*b*) 1-*p*-Methoxybenzoylthiosemicarbazide (22·0 g.) in N-sodium hydroxide (100 c.c.) reacted with methyl iodide (15·6 g.) in alcohol (20 c.c.) as in (*b*) above, giving the *S*-methyl*iso*thiosemicarbazide (22·0 g.) which crystallised from methyl alcohol in colourless needles (17·1 g.), m. p. 244° (decomp.).

The following were prepared by method (*b*): p-*nitrobenzoyl*-S-*methyl*- (II; R = *p*-NO_2·C_6H_4, R′ = H), golden-yellow plates (from alcohol), m. p. 176° (decomp.) (solidifies and remelts at 206°) (Found: C, 42·1; H, 3·7; S, 12·7. $C_9H_{10}O_3N_4S$ requires C, 42·5; H, 3·9; S, 12·6%), 1-p-*chlorobenzoyl*-S-*methyl*- (II; R = *p*-C_6H_4Cl, R′ = H), colourless needles (from ethyl acetate), m. p. 248—252° (decomp.) (Found: C, 44·6; H, 4·2; S, 12·9. $C_9H_{10}ON_3SCl$ requires C, 44·4; H, 4·1; S, 13·2%), 1-*benzoyl*-4 : S-*dimethyl*- (II; R = Ph, R′ = Me), colourless needles (from ethyl acetate), m. p. 140° decomp.) (Found: C, 53·7; H, 5·6; S, 14·3. $C_{10}H_{13}ON_3S$ requires C, 53·8; H, 5·8; S, 14·3%), 1-*benzoyl*-S-*methyl*-4-iso*propyl*- (II; R = Ph, R′ = Pr^i), colourless needles (from alcohol–ethyl acetate), m. p. 145° (decomp.) (Found: C, 57·8; H, 6·8; S, 13·1. $C_{12}H_{17}ON_3S$ requires C, 57·4; H, 6·8; S, 12·8%), 1-p-*methoxybenzoyl*-4 : S-*dimethyl*- (II; R = *p*-MeO·C_6H_4, R′ = Me), colourless needles (from ethyl acetate containing a little alcohol), m. p. 166° (decomp.) (Found: C, 52·2; H, 6·2. $C_{11}H_{15}O_2N_3S$ requires C, 52·2; H, 5·9%), and 1-*benzoyl*-4-*phenyl*-S-*methyl*-iso*thiosemicarbazide* (II; R = R′ = Ph), colourless refractive needles (from ethyl acetate–alcohol), m. p. 205—207° (decomp.) (Found: C, 63·1; H, 5·4; S, 11·2. $C_{15}H_{15}ON_3S$ requires C, 63·2; H, 5·3; S, 11·2%). In the last case, concentration of the crystallisation liquors gave the (sulphur-free) oxadiazole, m. p. 212° (Found: C, 70·4; H, 4·6. $C_{14}H_{11}ON_3$ requires C, 70·8; H, 4·6%) (see below).

2-*Amino*-5-*phenyl*-1 : 3 : 4-*oxadiazole* (III; R = Ph, R′ = H).—1-Benzoyl-*S*-methyl*iso*thiosemicarbazide (1·0 g.) was heated in an oil-bath at 200°. Methanethiol was rapidly evolved and after 10 minutes the residue was cooled and crystallised from alcohol, giving sheaves of colourless needles (0·65 g.), m. p. 242°, not depressed by admixture with a specimen prepared by the method of Fehrenbach and Stollé (*loc. cit.*) (Found: C, 59·8; H, 4·1. Calc. for $C_8H_7ON_3$: C, 59·6; H, 4·3%).

2-*Amino*-5-p-*methoxyphenyl*-1 : 3 : 4-*oxadiazole* (III; R = *p*-MeO·C_6H_4, R′ = H).—(*a*) *p*-Methoxybenzoyl-*S*-methyl*iso*thiosemicarbazide (1·2 g.) was heated for 0·25 hour at 190° and then by crystallisation from alcohol gave the *oxadiazole* as colourless needles (0·85 g.), m. p. 248—249° (Found: C, 56·8; H, 5·0. $C_9H_9O_2N_3$ requires C, 56·6; H, 4·7%).

(*b*) *p*-Methoxybenzoylthiosemicarbazide (5·6 g.), litharge (35·0 g.), and alcohol (750 c.c.) were heated under reflux for 24 hours and then filtered. The solvents were removed in a vacuum, and the residue was crystallised from alcohol giving colourless needles (1·6 g.), m. p. 248° not depressed by the compound prepared as in (*a*) (Found: C, 56·4; H, 4·9%).

2-*Amino*-5-p-*chlorophenyl*-1 : 3 : 4-*oxadiazole* (III; R = *p*-C_6H_4Cl, R′ = H).—(*a*) 1-*p*-Chlorobenzoyl-*S*-methyl*iso*thiosemicarbazide (1·0 g.) was heated for 0·25 hour at 200°; the residue, crystallised from alcohol, gave the *product* as large highly-refractive pale yellow prisms (0·5 g.), m. p. 274° (Found: C, 49·0; H, 2·9. $C_9H_6ON_3Cl$ requires C, 49·1; H, 3·1%).

(*b*) 1-*p*-Chlorobenzoylthiosemicarbazide (2·8 g.), alcohol (350 c.c.), and litharge (18·0 g.) gave, as in (*b*) (preceding compound), pale yellow prisms (0·7 g.), m. p. 272—274°, not depressed by the compound prepared as in (*a*) (Found: C, 49·1; H, 3·2%).

The following were obtained from the *S*-methyl*iso*thiosemicarbazides by heating for 0·25—0·5 hour at 135—140°. 2-*Methylamino*- (III; R = Ph, R′ = Me), colourless glistening plates (from benzene), m. p. 154° (Found: C, 62·5; H, 5·1. $C_9H_9ON_3$ requires C, 61·8; H, 5·1%), 2-iso*propylamino*- (III; R = Ph, R′ = Pr^i), colourless needles (from benzene), m. p. 139° (Found: C, 64·8; H, 6·2. $C_{11}H_{13}ON_3$

requires C, 65·0; H, 6·4%), and 2-*anilino*-5-*phenyl*-1 : 3 : 4-*oxadiazole* (III; R = R′ = Ph), large colourless needles, m. p. 210°, from alcohol (Found : C, 71·1; H, 4·7%).

2-*Methylthio*-5-*phenyl*-1 : 3 : 4-*oxadiazole* (IV; R = Ph).—(*a*) A mixture of syrupy phosphoric acid (20 c.c.) and phosphoric oxide (*ca.* 5·0 g.) was stirred and heated in a bath at 120°, while 1-benzoyl-*S*-methyl*iso*thiosemicarbazide (4·1 g.) was added during 0·5 hour. Benzoic acid, m. p. 120°, sublimed. Stirring and heating were continued for 0·5 hour, the residue diluted with ice–water, and the oil extracted with ether. The aqueous acid liquid gave, on being basified at 0—5°, a solid which was collected and crystallised from ethyl acetate, giving 1-benzoyl-*S*-methyl*iso*thiosemicarbazide as large colourless prisms (0·4 g.), m. p. 236° (Found : C, 51·4; H, 5·0%). In other experiments (heating at 125—130°) this acid liquor gave 2-amino-5-phenyl-1 : 3 : 4-oxadiazole, which crystallised from alcohol in colourless needles (0·4 g.), m. p. 242° (Found : C, 59·9; H, 4·2%). The ethereal extracts were shaken with 10% sodium carbonate solution, and the alkaline washes made acid, giving benzoic acid (0·5 g.), m. p. 121° (from water). The residual ethereal solution was dried and distilled, giving 2-*methylthio*-5-*phenyl*-1 : 3 : 4-*oxadiazole* as a colourless oil, b. p. 180—182°/20 mm., setting to a mass of colourless prisms (2·5 g.), m. p. 38°. From light petroleum (b. p. 40—60°) long colourless needles, m. p. 39°, were obtained on cooling to 0° (Found : C, 56·3; H, 4·0; N, 14·5; S, 16·5. $C_9H_8ON_2S$ requires C, 56·25; H, 4·2; N, 14·6; S, 16·7%). When the above experiment was repeated with 95% sulphuric acid (22·0 c.c.) in place of the phosphoric acid–phosphoric oxide, only benzoic acid (2·2 g.; m. p. 120°) was isolated. A smaller yield of methylthio-oxadiazole (1·5 g.) was obtained with syrupy phosphoric acid alone.

(*b*) 1-Benzoyl-4 : *S*-dimethyl*iso*thiosemicarbazide (6·6 g.) and phosphoric acid (30 c.c.), as in (*a*), gave benzoic acid (0·5 g.), m. p. 121°, and 2-methylthio-5-phenyl-1 : 3 : 4-oxadiazole (0·8 g.), m. p. 38°. The precipitate obtained on basifying the phosphoric acid liquors (3·5 g.) was crystallised slowly from benzene–light petroleum (b. p. 60—80°), whereupon small colourless needles separated. The mother-liquor was carefully decanted and the residue repeatedly crystallised from the same solvent mixture, giving 2-methylamino-5-phenyl-1 : 3 : 4-oxadiazole (0·9 g.), m. p. 153° (Found : C, 61·6; H, 5·1%). The original benzene–light petroleum liquor was allowed to crystallise further, giving a mixture of large colourless plates and more small needles. The plates were separated by hand (1·6 g.) and recrystallised, giving 5-*methylthio*-3-*phenyl*-4-*methyl*-4 : 1 : 2-*triazole* (1·4 g.), m. p. 138° (Found : C, 58·6; H, 5·0. $C_{10}H_{11}N_3S$ requires C, 58·5; H, 5·4%). This triazole was also obtained by treating the parent thiol (0·9 g.) in alcohol (7·0 c.c.) at 60° with methyl iodide (0·8 g.) in alcohol (3·0 c.c.) in a closed vessel. After 12 hours, ether (10·0 c.c.) was added, the hydriodide collected and decomposed with N-sodium hydroxide, the solid dissolved in N-hydrochloric acid, filtered (charcoal), and precipitated with sodium hydroxide. The solid (0·6 g.; m. p. 136°) was crystallised from benzene–light petroleum, giving large colourless plates (0·4 g.), m. p. 136—137° (Found : C, 58·6; H, 5·3%).

(*c*) 1-Benzoyl-*S*-methyl-4-*iso*propyl*iso*thiosemicarbazide (4·4 g.), phosphoric acid (20 c.c.), and phosphoric oxide (5·0 g.) gave, as in (*a*), 2-methylthio-5-phenyl-1 : 3 : 4-oxadiazole (0·5 g.), m. p. 38° (Found : C, 56·5; H, 4·2%), and benzoic acid (0·4 g.). Neutralisation of the acid mother-liquors gave unchanged starting material (2·6 g.), m. p. 142° (after crystallisation from ethyl acetate containing a little alcohol) (Found : S, 12·6%).

2-*Methylthio*-5-p-*methoxyphenyl*-1 : 3 : 4-*oxadiazole* (IV; R = *p*-MeO·C_6H_4).—(*a*) 1-*p*-Methoxybenzoyl-*S*-methyl*iso*thiosemicarbazide (10·0 g.) was added to a mixture of phosphoric acid (40 c.c.) and phosphoric oxide (10·0 g.) at 110—115° (at 120° much charring took place) during 0·5 hour. After a further 0·25 hour at 115° some effervescence took place and the mixture was at once poured on ice. The precipitate was collected, washed with water, suspended in 10% sodium carbonate solution, and filtered. The filtrate, on acidification, gave *p*-anisic acid (2·6 g.), which crystallised from water in colourless needles, m. p. 182°. The insoluble residue was crystallised from light petroleum (b. p. 60—80°), giving 2-*methylthio*-5-p-*methoxyphenyl*-1 : 3 : 4-*oxadiazole* as colourless needles (2·2 g.), m. p. 100—101° (Found : C, 54·0; H, 4·4; N, 12·5; S, 14·3. $C_{10}H_{10}O_2N_2S$ requires C, 54·1; H, 4·5; N, 12·6; S, 14·4%). Basifying the phosphoric acid liquors gave 1-*p*-methoxybenzoyl-*S*-methyl*iso*thiosemicarbazide which crystallised from alcohol in long colourless needles (2·1 g.), m. p. 246° (Found : C, 50·5; H, 5·4%).

(*b*) 1-*p*-Methoxybenzoyl-4 : *S*-dimethyl*iso*thiosemicarbazide treated, as in (*a*), gave the same methylthio-oxadiazole, m. p. 100° (Found : C, 53·9; H, 4·3%).

2-*Methylthio*-5-p-*chlorophenyl*-1 : 3 : 4-*oxadiazole* (IV; R = *p*-C_6H_4Cl).—1-*p*-Chlorobenzoyl-*S*-methyl*iso*thiosemicarbazide (4·9 g.), phosphoric acid (20·0 c.c.), and phosphoric oxide, allowed to react at 120° as in method (*a*) for the *p*-methoxybenzoyl compound, gave the *methylthio-oxadiazole* which crystallised from light petroleum (b. p. 60—80°) as large colourless plates (1·5 g.), m. p. 119° (Found : C, 47·5; H, 3·0. $C_9H_7ON_2ClS$ requires C, 47·8; H, 3·1%). 1-*p*-Chlorobenzoyl-*S*-methyl*iso*thiosemicarbazide was isolated from the acid liquors and crystallised from ethyl acetate, giving colourless needles (1·0 g.), m. p. 254° (Found : C, 44·7; H, 4·3; S, 13·2%).

2-*Methanesulphonyl*-5-*phenyl*-1 : 3 : 4-*oxadiazole* (V; R = Ph).—2-Methylthio-5-phenyl-1 : 3 : 4-oxadiazole (6·5 g.) in acetic acid (50 c.c.) was stirred while potassium permanganate (11·0 g.) in water (170 c.c.) was added during 1 hour, the temperature being kept at 30—35°. After stirring for a further hour, the reaction liquid was cooled to 0° and decolorised with sulphur dioxide, and the solid collected. After being dried in a vacuum over phosphoric oxide, the *sulphone* crystallised from light petroleum (b. p. 80—100°) containing a little benzene as colourless needles (5·5 g.), m. p. 133—134° (Found : C, 48·5; H, 4·0; S, 14·3. $C_9H_8O_3N_2S$ requires C, 48·2; H, 3·6; S, 14·3%).

2-*Methanesulphonyl*-5-p-*methoxyphenyl*-1 : 3 : 4-*oxadiazole* (V; R = *p*-MeO·C_6H_4).—Crystallised from benzene, this *product* formed flat colourless needles, m. p. 184° (Found : C, 47·3; H, 4·0; S, 12·3. $C_{10}H_{10}O_4N_2S$ requires C, 47·2; H, 3·9; S, 12·6%).

2-*Methanesulphonyl*-5-p-*chlorophenyl*-1 : 3 : 4-*oxadiazole* (V; R = *p*-C_6H_4Cl).—2-Methylthio-5-*p*-chlorophenyl-1 : 3 : 4-oxadiazole (6·9 g.) was oxidised in acetic acid (100 c.c.) with potassium permanganate (9·0 g.) in water (150 c.c.) as above. After removal of manganese dioxide at 0°, the white solid was collected and triturated with ice-cold 5% sodium carbonate solution. The alkaline filtrate was treated with hydrochloric acid, and the precipitated *p*-chlorobenzoic acid (0·5 g.) crystallised from benzene, giving colourless glistening needles, m. p. 238—240° not depressed by an authentic sample (Found : C,

53·4; H, 3·2. Calc. for $C_7H_5O_3Cl$: C, 53·7; H, 3·2%). The residue insoluble in sodium carbonate solution was dried in a vacuum and crystallised from benzene, giving the *oxadiazole* as colourless felted needles (4·9 g.), m. p. 160° (Found: C, 42·1; H, 2·9; S, 12·6. $C_9H_7O_3N_2ClS$ requires C, 41·7; H, 2·7; S, 12·4%). The *p*-chlorobenzoic acid is not formed by the action of the sodium carbonate, as direct crystallisation gave a mixture of the sulphone and the acid, separated in part by hand picking.

2-*Hydroxy*-5-*phenyl*-1 : 3 : 4-*oxadiazole* (VI; R = Ph).—2-Methanesulphonyl-5-phenyl-1 : 3 : 4-oxadiazole (1·0 g.) was ground with N-sodium hydroxide (10 c.c.), filtered (charcoal), and treated with concentrated hydrochloric acid. The solid was collected and crystallised from water, giving the *hydroxy*-compound as long silky needles (0·65 g.), m. p. 135—136° (Found: C, 59·5; H, 3·9. $C_8H_6O_2N_2$ requires C, 59·3; H, 3·7%).

Similar experiments and crystallisation from benzene–light petroleum (b. p. 60—80°) gave 2-*hydroxy*-5-p-*methoxyphenyl*- (VI; R = *p*-MeO·C_6H_4), colourless flat needles, m. p. 184° (Found: C, 56·0; H, 4·1. $C_9H_8O_3N_2$ requires C, 56·3; H, 4·2%), and 2-*hydroxy*-5-p-*chlorophenyl*-1 : 3 : 4-*oxadiazole* (VI; R = *p*-C_6H_4Cl), colourless, flat, glistening needles, m. p. 226—227° (Found: C, 48·6; H, 2·6. $C_8H_5O_2N_2Cl$ requires C, 48·9; H, 2·5%).

2-iso*Propylamino*-5-*phenyl*-1 : 3 : 4-*oxadiazole* (III; R = Ph, R′ = Pr^i).—2-Methanesulphonyl-5-phenyl-1 : 3 : 4-oxadiazole (1·1 g.) and *iso*propylamine (0·6 g.; dried over sodium) were heated in a sealed tube for 0·5 hour at 100°. The residue was dissolved in N-hydrochloric acid (100 c.c.), filtered (charcoal), and treated with sodium hydroxide, giving a solid which was collected and dried in a vacuum (0·7 g.) and then melted at 136—137°. Crystallisation from benzene gave long colourless needles (0·5 g.), m. p. 138—139° not depressed by admixture with the compound as prepared above (Found: C, 64·9; H, 6·1%).

2-2′-*Diethylaminoethylamino*-5-*phenyl*-1 : 3 : 4-*oxadiazole* (III; R = Ph, R′ = $[CH_2]_2$·NEt_2).—Powdered 2-methanesulphonyl-5-phenyl-1 : 3 : 4-oxadiazole (3·3 g.) was cautiously added to dry 2-diethylaminoethylamine (2·7 g.; dried over sodium) at 80° during 10 minutes, so that the temperature did not rise above 100°. After a further 10 minutes, the melt was cooled and dissolved in 10% acetic acid and filtered (charcoal); sodium hydroxide precipitated an oil, which was extracted with ether, dried (Na_2SO_4), and distilled, giving the *amine* as a colourless oil, b. p. 192—194°/0·01 mm., setting to a crystalline mass (3·1 g.), m. p. 40—42°. From light petroleum (b. p. 40—60°), colourless leaflets separated on cooling in ice, m. p. 48° (Found: C, 64·9; H, 7·3; N, 21·4. $C_{14}H_{20}ON_4$ requires C, 64·6; H, 7·7; N, 21·5%). The *picrate* separated from alcohol in yellow needles, m. p. 176°, which on recrystallisation gave deep orange prisms, m. p. 178° (Found: C, 48·9; H, 4·6. $C_{14}H_{20}ON_4$,$C_6H_3O_7N_3$ requires C, 49·1; H, 4·7%).

The following were prepared from the corresponding sulphones in similar experiments. 2-2′-*Diethylaminoethylamino*-5-p-*methoxyphenyl*-1 : 3 : 4-*oxadiazole* (III; R = *p*-MeO·C_6H_4, R′ = $[CH_2]_2$·NEt_2) crystallised in colourless needles or leaflets from benzene–light petroleum (b. p. 60—80°), m. p. 107° (Found: C, 62·1; H, 7·5. $C_{15}H_{22}O_2N_4$ requires C, 62·1; H, 7·6%), and gave a *picrate* golden-yellow needles (from alcohol), m. p. 175—176° (Found: C, 47·1, 46·9; H, 5·1, 4·6. $C_{15}H_{22}O_2N_4$,$C_6H_3O_7N_3$,H_2O requires C, 46·9; H, 5·0%). 2-2′-*Diethylaminoethylamino*-5-p-*chlorophenyl*-1 : 3 : 4-*oxadiazole* (III; R = *p*-C_6H_4Cl, R′ = $[CH_2]_2$·NEt_2) crystallised in large colourless glistening plates, m. p. 99° (Found: C, 56·6; H, 6·1. $C_{14}H_{19}ON_4Cl$ requires C, 57·0; H, 6·4%).

5-*Ethoxy*-3-*phenyl*-1 : 2 : 4-*triazole* (VII; R = Ph, R′ = Et).—1-Benzoyl-*S*-methyl*iso*thiosemicarbazide (8·4 g.) was heated under reflux with a solution of sodium (1·5 g.) in alcohol (200 c.c.) for 3 hours, the solvent removed under reduced pressure, and the residue shaken well with ice and water and filtered off. The residue (2·8 g.; m. p. 238—240°) was crystallised from alcohol, giving 2-amino-5-phenyl-1 : 3 : 4-oxadiazole as colourless sheaves of needles (1·5 g.), m. p. 242—243° (Found: C, 59·8; H, 4·6%). The alkaline mother-liquors were cooled strongly, made just acid with acetic acid, the precipitate allowed to harden, collected, and dissolved in hot N-sodium hydroxide (100 c.c.). After filtration (charcoal), an excess of strong hydrochloric acid was added to the cold solution until the first-formed precipitate was dissolved. The solution was again filtered (charcoal) and made just alkaline (potassium hydrogen carbonate), and the triazole was collected, dried in a vacuum, and crystallised from light petroleum (b. p. 100—120°), giving clumps of large glistening needles (1·0 g.), m. p. 116—117° (Found: C, 63·8; H, 5·8; N, 22·0. $C_{10}H_{11}ON_3$ requires C, 63·5; H, 5·8; N, 22·2%).

5-*Ethoxy*-3-p-*methoxyphenyl*-1 : 2 : 4-*triazole* (VII; R = *p*-MeO·C_6H_4, R′ = Et).—1-*p*-Methoxybenzoyl-*S*-methyl*iso*thiosemicarbazide (9·1 g.) gave, as in the preceding experiment, 2-amino-5-*p*-methoxyphenyl-1 : 3 : 4-oxadiazole (3·35 g.), m. p. 250° (Found: C, 56·6; H, 4·8%), and the *ethoxy-triazole* which crystallised from benzene in small colourless rectangular plates (2·8 g.), m. p. 146° (Found: C, 59·9; H, 6·1; N, 19·5. $C_{11}H_{13}O_2N_3$ requires C, 60·3; H, 5·9; N, 19·2%). This ethoxy-triazole was much less soluble in dilute hydrochloric acid than was the 3-phenyl analogue.

5-*Ethoxy*-3-p-*chlorophenyl*-1 : 2 : 4-*triazole* (VII; R = *p*-C_6H_4Cl, R′ = Et).—1-*p*-Chlorobenzoyl-*S*-methyl*iso*thiosemicarbazide (4·9 g.) and a solution of sodium (0·75 g.) in alcohol (100 c.c.) gave 2-amino-5-*p*-chlorophenyl-1 : 3 : 4-oxadiazole (0·7 g.), m. p. 270° (Found: C, 49·3; H, 3·3%), and the *ethoxy-triazole* which crystallised from benzene in clumps of colourless needles (1·6 g.), m. p. 148° (Found: C, 53·3; H, 4·5. $C_{10}H_{10}ON_3Cl$ requires C, 53·7; H, 4·5%). The ethoxy-triazole was not sufficiently soluble in dilute acid to be purified in the way used above and was, probably for this reason, difficult to crystallise.

5-*Methoxy*-3-p-*methoxyphenyl*-1 : 2 : 4-*triazole* (VII; R = *p*-MeO·C_6H_4, R′ = Me).—This *compound* was obtained in the same way as the corresponding ethoxy-compound, by use of sodium methoxide and crystallised from benzene in large colourless prisms, m. p. 164° (Found: C, 58·3; H, 5·3. $C_{10}H_{11}O_2N_3$ requires C, 58·5; H, 5·4%).

5-*Hydroxy*-3-*phenyl*-1 : 2 : 4-*triazole* (VII; R = Ph, R′ = H).—(*a*) 3-Ethoxy-5-phenyl-1 : 2 : 4-triazole (0·9 g.) was heated under reflux with concentrated hydrochloric acid (25 c.c.) for 0·5 hour. After initial dissolution, crystals quickly separated and after cooling were collected, washed with water, and crystallised from alcohol, giving colourless needles (0·5 g.), m. p. 324° (Young and Witham, *loc. cit.*, give m. p. 321—322°) (Found: C, 59·7; H, 4·6. Calc. for $C_8H_7ON_3$: C, 59·6; H, 4·3%). This compound (0·3 g.), fused sodium acetate (0·3 g.), and acetic anhydride (4·0 c.c.) were heated under reflux for 5 minutes and then poured into water and the acetyl derivative crystallised from alcohol, giving large colourless needles

(0·2 g.), m. p. 248° (Young and Witham give m. p. 248°) (Found : C, 59·3; H, 4·7; N, 21·1. Calc. for $C_{10}H_9O_2N_3$: C, 59·1; H, 4·4; N, 20·7%).

(*b*) Benzaldehyde semicarbazone (5·5 g.), alcohol (25 c.c.), water (0·5 c.c.), and ferric chloride (anhydrous; 5·5 g.) were heated in a sealed tube at 135—140° for 2 hours, cooled, and diluted with water (200 c.c.). The solid was collected and stirred with N-sodium hydroxide for 0·5 hour. The filtrate was made acid (hydrochloric acid), and the solid collected, washed, and crystallised from alcohol, giving colourless needles of the hydroxy-triazole (1·1 g.), m. p. 324° not depressed by the compound as prepared above (Found : C, 59·4; H, 4·4%). The acetate, prepared as previously, crystallised from alcohol in colourless needles, m. p. 248°. The insoluble material left after the initial extraction with sodium hydroxide solution was stirred with N-hydrochloric acid. Nothing was extracted and the residue of benzaldehyde azine was crystallised from alcohol in yellow plates (1·0 g.), m. p. 90° not depressed by admixture with an authentic sample.

5-Hydroxy-3-p-methoxyphenyl-1 : 2 : 4-triazole (VII; R = *p*-MeO·C_6H_4, R′ = H).—(*a*) 3-Ethoxy-5-*p*-methoxyphenyl-1 : 2 : 4-triazole (1·0 g.) gave, by acid treatment, the *hydroxy-triazole* which was crystallised from 2-ethoxyethanol and then from acetic acid, giving small colourless leaflets (0·85 g.), m. p. 334° (Found : C, 56·7; H, 4·7. $C_9H_9O_2N_3$ requires C, 56·5; H, 4·7%). The *acetate* was formed as above and crystallised from alcohol giving fine hair-like needles, m. p. 226° (Found : C, 56·5; H, 4·8. $C_{11}H_{11}O_3N_3$ requires C, 56·65; H, 4·7%). The hydroxy-triazole (0·3 g.), m. p. 334° (Found : C, 56·5; H, 4·8%), was also obtained by the action of acid on 3-methoxy-5-*p*-methoxyphenyl-1 : 2 : 4-triazole (0·5 g.).

(*b*) Oxidation of *p*-methoxybenzaldehyde semicarbazone (9·7 g.) with ferric chloride (8·5 g.) in alcohol (50 c.c.) and water (1·0 c.c.), as described for the benzylidene compound, gave the hydroxy-triazole which crystallised from acetic acid in colourless leaflets (2·1 g.), m. p. 336° (Found : C, 56·3; H, 4·7%). The acetate crystallised from alcohol in fine colourless needles, m. p. 226° (Found : C, 56·4; H, 4·9%). *p*-Methoxybenzaldehyde azine, which crystallised from xylene in yellow needles (1·4 g.), m. p. 170° not depressed by an authentic sample, was also isolated.

5-Hydroxy-3-p-chlorophenyl-1 : 2 : 4-triazole (VII; R = *p*-C_6H_4Cl, R′ = H).—(*a*) 3-Ethoxy-5-*p*-chlorophenyl-1 : 2 : 4-triazole (0·9 g.) gave, with acid, the *hydroxy-triazole* which was crystallised from acetic acid in long silky needles (0·5 g.), m. p. 402—404° (Found : C, 49·0; H, 3·1. $C_8H_6ON_3Cl$ requires C, 49·1; H, 3·1%).

(*b*) Oxidation of *p*-chlorobenzaldehyde semicarbazone (1·9 g.) with ferric chloride (1·5 g.) in alcohol (10 c.c.) and water (1·0 c.c.) gave the hydroxy-triazole, which crystallised from acetic acid in colourless needles (0·3 g.), m. p. 406° (Found : C, 49·2; H, 2·8%), and *p*-chlorobenzaldehyde azine which crystallised from alcohol in golden leaflets (0·6 g.), m. p. 208° (Pascal, and Normand, *Bull. Soc. chim.*, 1911, **9**, 1061, give m. p. 211°) (Found : C, 60·4; H, 3·7. Calc. for $C_{14}H_{10}N_2Cl_2$: C, 60·6; H, 3·6%).

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BLACKLEY, MANCHESTER, 9. [*Received, March 1st*, 1949.]

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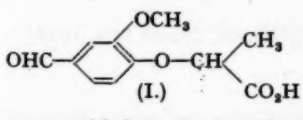
409. *The Preparation and Resolution of an Externally Compensated Formyl Acid.*

By G. R. CLEMO, W. A. CUMMINGS, and R. RAPER.

α-(2-Methoxy-4-formylphenoxy)propionic acid has been prepared and resolved into its (+)- and (−)-forms by fractional crystallisation of its cinchonine salt.

IN general, the resolution of racemic aldehydes into their optically active forms involves combination with a reagent such as (+)- or (−)-menthylhydrazine (compare Galloway and Read, *J.*, 1936, 1222). Few such reagents are readily available and there are even fewer accounts in the literature of the use of optically active aldehydes in the resolution of substances with which they combine. Erlenmeyer (*Ber.*, 1903, **36**, 976) resolved 2-hydroxy-1 : 2-diphenylethylamine by combination with helicin, but a readily available optically active aldehyde which could be used to resolve neutral externally compensated compounds containing reactive methylene groups has obvious potential uses, and we have directed our attention to the preparation of such a compound.

Sodium vanilloxide (Meldrum and Patel, *J. Indian Chem. Soc.*, 1928, **5**, 191) was condensed with ethyl α-bromopropionate in dry alcoholic solution to give *ethyl α-(2-methoxy-4-formylphenoxy)propionate*, which was hydrolysed by hydrochloric acid to give the free *acid* (I). The (−)-*acid* was obtained by crystallisation of the cinchonine salt, and had $[\alpha]_D^{25}$ −32·5°. An optically impure (+)-acid having $[\alpha]_D$ −7·9° was obtained from the quinine salt, and repeated attempts to prepare the optically pure acid by varying the conditions of crystallisation of this salt were unsuccessful. If, however, the aqueous mother-liquors from the crystallisation of the cinchonine salt of the (−)-acid were concentrated to small volume and this salt separated as completely as possible, the much more soluble salt of the (+)-acid remained in solution, and the (+)-acid, $[\alpha]_D^{15}$ +33·0°,



(I.)

was obtained on removal of the alkaloid. A mixture of equal amounts of the (+)- and the (−)-acid regenerated the externally compensated acid. When the pure (+)-*acid* was combined with quinine, a *salt* was obtained which did not crystallise satisfactorily, and prolonged boiling of its solution did not bring about racemisation. It is probable, therefore, that the failure to resolve the (±)-acid by means of quinine is due to the formation of a partly racemic salt contaminated with varying amounts of the salt of the (+)-acid. The (±)-acid did not form salts with brucine or strychnine.

Experimental.

Ethyl α-(2-Methoxy-4-formylphenoxy)propionate.—Sodium vanilloxide (50 g.) and ethyl α-bromopropionate (42·0 g.) in absolute alcohol (400 ml.) were heated under reflux in an oil-bath at 120—125° for 45 hours. The solution was cooled and filtered, the alcohol distilled off, and sodium bromide, which crystallised, removed. The residual yellow oil was distilled, giving *ethyl α-(2-methoxy-4-formylphenoxy)-propionate* as a colourless viscous oil (35·4 g.), b. p. 166—167°/3 mm. When kept it set to a waxy white solid (Found: C, 61·9; H, 6·5. $C_{13}H_{16}O_5$ requires C, 61·9; H, 6·35%). The 2 : 4-*dinitrophenylhydrazone* crystallises in very small prisms from alcohol; m. p. 164—165° (Found: C, 52·6; H, 4·45. $C_{19}H_{20}O_8N_4$ requires C, 52·7; H, 4·6%).

α-(2-Methoxy-4-formylphenoxy)propionic Acid.—The above ester (13·7 g.) in absolute alcohol (41 ml.) and concentrated aqueous hydrochloric acid (41 ml.) were kept at room temperature for 3 days. The mixture was diluted with water (100 ml.), and the alcohol evaporated; on cooling and scratching, a white crystalline solid was deposited which was purified by dissolving it in dilute sodium carbonate solution, filtering from unchanged ester, and reprecipitating it with concentrated aqueous hydrochloric acid. The free *acid* (10·6 g.) crystallised from benzene–light petroleum (b. p. 60—80°) as fine hygroscopic needles, m. p. 79—80° (Found: C, 59·1; H, 5·5. $C_{11}H_{12}O_5$ requires C, 58·9; H, 5·4%).

Cinchonine salt. Cinchonine (15·16 g.) and the (±)-acid (11·54 g.) were heated under reflux in water (1220 ml.) for 1 hour and filtered. The crystals deposited on cooling were collected and fractionally crystallised from water. The mother-liquor (*M*) was set aside (see below). The final fraction after 5 crystallisations of the *salt* had $[\alpha]_D^{15}$ +77·35° (*c* = 1·049 in alcohol, *l* = 1) (Found: C, 63·5; H, 6·7; N, 5·1. $C_{30}H_{34}O_6N_2,3H_2O$ requires C, 62·9; H, 7·05; N, 4·9%).

(−)-α-(2-Methoxy-4-formylphenoxy)propionic Acid.—The final fraction of the cinchonine salt was shaken with excess of sodium carbonate solution (33%). The cinchonine was filtered off, and the aqueous solution extracted 15 times with chloroform to ensure complete removal of the cinchonine. The solution of the sodium salt was acidified with concentrated hydrochloric acid, and the precipitated (−)-*acid* collected, washed, and dried. The aqueous solution, when extracted with ether, gave a further quantity of (−)-acid, which crystallised from benzene–light petroleum in fine colourless needles, m. p. 89—90°; α_D^{15} −0·328° (*l* = 1, *c* = 1·008 in alcohol), $[\alpha]_D^{15}$ −32·5° (Found: C, 58·6; H, 5·4. $C_{11}H_{12}O_5$ requires C, 58·9; H, 5·4%).

(+)-α-(2-Methoxy-4-formylphenoxy)propionic Acid.—The mother-liquors (*M*) were concentrated to 100 ml., and the white solid crystallising out removed; when the filtrate was concentrated to 50 ml., no further solid separated. The solution was shaken with excess of sodium carbonate, and the (+)-*acid* recovered as described for the (−)-acid. It crystallised from benzene–light petroleum as fine colourless needles, m. p. 89—90°, α_D^{15} +0·301° (*l* = 1, *c* = 0·912 in alcohol), $[\alpha]_D^{15}$ 33·0° (Found: C, 58·9; H, 5·3%).

A mixture of 0·0715 g. each of the (+)- and the (−)-acid made up to 10 ml. in absolute alcohol was inactive. The (±)-acid recovered from this measurement had m. p. 78—79°, not depressed on admixture with authentic (±)-acid, m. p. 79—80°.

Quinine salt. (*a*) Quinine (12·94 g.) and (±)-acid (8·97 g.) were heated under reflux in water (600 ml.) for 2 hours and filtered. The crystals deposited on cooling were collected and dried. The *salt* was fractionally crystallised from water, the final fraction after 6 crystallisations having $[\alpha]_D^{18}$ −86·8° (*c* = 8·68 in alcohol, *l* = 1) (Found: C, 63·8; H, 6·4. $C_{31}H_{36}O_7N_2,2H_2O$ requires C, 63·7; H, 6·9%). The acid was recovered from the final fraction similarly to the (−)-acid; m. p. 84—85°; α_D^{16} +0·103° (*l* = 1, *c* = 0·76 in alcohol), $[\alpha]_D^{16}$ +13·2° (Found: C, 58·7; H, 5·6%).

(*b*) Quinine (7·088 g.), (±)-acid (11·1984 g.), and sodium carbonate (1·1595 g.) were heated under reflux in water (750 ml.) for 4 hours and concentrated to 500 ml.; the crystals which separated were collected and dried. The salt was fractionally crystallised from water, the final fraction after 6 crystallisations having $[\alpha]_D^{15}$ −80·9° (*c* = 8·18 in absolute alcohol, *l* = 1) (Found: C, 63·9; H, 6·8%). The acid, recovered from the final fraction similarly to the (−)-acid, had m. p. 81—82°; α_D^{15} +0·0825° (*l* = 1, *c* = 1·04 in alcohol), $[\alpha]_D^{15}$ +7·9° (Found: C, 59·3; H, 5·7%).

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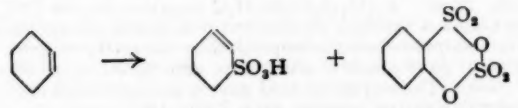
410. *Reactions of Cyclic Hydrocarbons. Part I. The Sulphonation of cyclo*Hexene *and* 1-*Methylcyclo*pentene.*

By R. Sperling.

Sulphonation of *cyclo*hexene with the dioxan–sulphur trioxide complex gave *cyclo*hexene-3-sulphonic acid and anydro-*trans*-2-sulpho*cyclo*hexyl hydrogen sulphate, whereas 1-methyl-*cyclo*pentene gave 1-methyl*cyclo*pentene-5-sulphonic acid and some unsaturated disulphonic acids.

The sulphonation of olefins by means of dioxan–sulphur trioxide complex suspended in ethylene dichloride has been extensively investigated by Suter and his collaborators (*J. Amer. Chem. Soc.*, 1938, **60**, 538; 1941, **63**, 978, 1594; 1943, **65**, 507; 1944, **66**, 1105; 1945, **67**, 827). According to the nature of the olefin, they obtained unsaturated sulphonic acids or sulphated hydroxysulphonic acids, the reaction being accompanied by little polymerisation or other side-reactions.

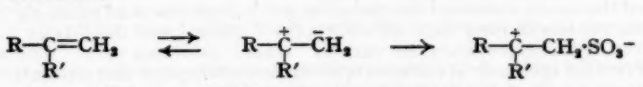
Such treatment of *cyclo*hexene resulted in the formation of *cyclo*hexene-3-sulphonic acid (I) as principal product, which was accompanied by anhydro-*trans*-2-sulpho*cyclo*hexyl hydrogen sulphate (II) and a small amount of similar derivatives from the dimer, *cyclo*hexenyl*cyclo*hexane.



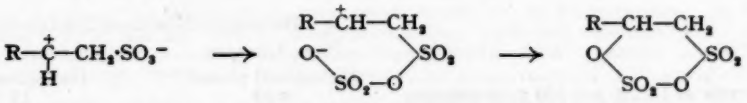
(I.) (II.)

1-Methyl*cyclo*pentene, which can be regarded as a possible isomerisation product of *cyclo*hexene (cf. Block and Thomas, *J. Amer. Chem. Soc.*, 1944, **66**, 1589), gave 1-methyl*cyclo*pentene-5-sulphonic acid with some unsaturated disulphonic acids, whilst no anhydro sulphated hydroxysulphonic acids were produced. 1-Methyl*cyclo*pentene-5-sulphonic acid was much less stable than *cyclo*hexene-3-sulphonic acid, the carbon–sulphur bond being readily ruptured. This instability is probably due to the increased strain introduced into the five-membered ring by the double bond, and to the presence of the methyl group adjacent to the double bond.

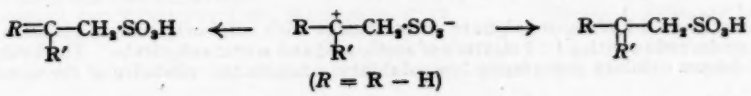
Bordwell, Suter, and Webber (*J. Amer. Chem. Soc.*, 1945, **67**, 827) concluded that the reaction between dioxan–sulphur trioxide complex and an olefin could be regarded as a nucleophilic replacement reaction:



If R or R′ were hydrogen, the next step would be addition of a second molecule of sulphur trioxide to give an anhydro sulphated hydroxy-sulphonic acid which would yield a hydroxysulphonic acid on hydrolysis:



If, however, R or R′ were alkyl or phenyl, the predominant reaction after the initial reaction would be migration of a proton to give unsaturated sulphonic acids, the proton being released from one of the carbon atoms adjacent to that bearing the positive charge:



(*R* = R − H)

The behaviour of *cyclo*hexene differs from that predicted above in that it tends to behave in a manner similar to that of an olefin in which two alkyl groups are attached to one of the

* The work described in Parts I—III of this series was carried out in partial fulfilment of the requirements of the University of London for the award of the Ph.D. Degree.

unsaturated carbon atoms, this being due probably to the increased activity of the α-methylenic hydrogen atom in *cyclo*hexene.

The production of 1-methyl*cyclo*pentene-5-sulphonic acid from 1-methyl*cyclo*pentene is in accordance with the predictions of Bordwell, Suter, and Webber, and lends support to their contention that the sulphonation of olefins is not brought about by substitution, which would have tended to result in the formation of 1-methyl*cyclo*pentene-3-sulphonic acid.

Experimental.

(M.p.s are corrected.)

cyclo*Hexene*.

Sulphonation of cyclo*Hexene*.—94·75 G. (1·15 mols.) of peroxide-free *cyclo*hexene were treated with 395 g. (2·3 mols.) of dioxan–sulphur trioxide in the presence of ethylene dichloride (400 ml.), the temperature being maintained at 0°. After 1 hour, the mixture was diluted with water, the ethylene dichloride layer removed, and the aqueous layer neutralised with barium hydroxide. The barium sulphate was removed by filtration, and the filtrate evaporated to small bulk under reduced pressure. The resulting barium salts were separated by fractional crystallisation from aqueous alcohol, and the following products separated in order of increasing solubility (total yields): *barium* cyclo*hexene*-3-*sulphonate*, 105·1 g.; *barium* 2-*sulpho*cyclo*hexyl hydrogen sulphate*, 55·4 g.; dimer derivatives, 30·8 g.

In addition, 6·3 g. of a *cyclo*hexene(?-4-)sulphonate was obtained.

cyclo*Hexene*-3-*sulphonic acid*. The barium salt crystallised in hexagonal plates analysing as the monohydrate (Found: Ba, 28·69. $C_{12}H_{18}S_2O_6Ba,H_2O$ requires Ba, 28·76%). It became anhydrous on heating to 120°. The aqueous solution decolorised potassium permanganate solution and bromine water, only a trace of barium sulphate being precipitated by the latter reagent. Oxidation with alkaline potassium permanganate at 0° gave glutaric acid, m. p. and mixed m. p. 96—98° (Found: equiv., 65. Calc. for $C_5H_8O_4$: equiv., 66). The sulphonic acid gave a benzylthiuronium salt, needles, m. p. 150—151°, and a phenylhydrazine derivative, needles, m. p. 141—143°.

Anhydro-"trans"-2-*sulpho*cyclo*hexyl hydrogen sulphate*. This compound was not isolated as such, but as its hydrolysis product in the form of barium "*trans*"-2-sulpho*cyclo*hexyl hydrogen sulphate (Found: 30·4. $C_6H_{10}S_2O_7Ba,3H_2O$ requires Ba, 30·53%), which could be further hydrolysed by heating in water at 125° for 4 hours. The resulting barium "*trans*"-*cyclo*hexanol-2-sulphonate was isolated as hexagonal plates, readily soluble in water and aqueous alcohol. It was acetylated by heating under reflux with a mixture of equal parts of acetic acid and acetic anhydride for 2 hours and sulphated by treatment with oleum at 0°. Oxidation with nitric acid (*d*, 1·26) gave adipic acid, m. p. and mixed m. p. 150—151°, giving a benzylthiuronium salt as needles, m. p. 156—157°.

The properties of this *cyclo*hexanol-2-sulphonic acid differed from those of the acid synthesised either from *cyclo*hexene oxide or from 2-chloro*cyclo*hexanol. Since the properties of the latter, *viz.*, low solubility in water and inability to form a benzylthiuronium derivative, indicated hydrogen bonding, it was decided to call it the "*cis*"-compound as it was considered that the proximity of the hydrogen atom of the hydroxyl group to one of the co-ordinated oxygen atoms of the sulphonic acid group in the case of "*cis*"-isomer would facilitate hydrogen bonding.

Consideration of the configuration of the *cyclo*hexanol-2-sulphonic acid molecule by means of Fischer–Hirschfelder atomic models showed that with both the "chair" and the "boat" configuration of the *cyclo*hexane ring, the distances between the various "*trans*"-positions vary. The same applies to the "*cis*"-isomers. Treating each pair of carbon atoms in the *cyclo*hexane ring separately, hydrogen bonding would be possible in only six of the twelve possible forms of the "*trans*"-isomer with the "chair" configuration, and in four of the twelve forms with the "boat" configuration. With the "*cis*"-isomer, bonding is possible in all twenty-four positions. Hydrogen bonding is thus favoured in the case of the "*cis*"-isomer.

The properties of the two isomers are compared in the table below.

	Barium *cyclo*hexanol-2-sulphonates,	
	"*cis*"-isomer.	"*trans*"-isomer.
Crystal form	Hexagonal plates	Hexagonal plates
Solubility in water at 18°, g. per 100 g. of solution	8·22	17·75
Benzylthiuronium salt	Not formed	Needles, m. p. 156—157°
Phenylhydrazine derivative	Diamond-shaped plates, m. p. 140—141°	Diamond-shaped plates, m. p. 158—159°
	(mixed m. p. 128—132°)	

Each isomer gives a hydrogen sulphate on treatment with sulphuric acid or oleum, and an acetate on heating it under reflux with a 1 : 1 mixture of acetic acid and acetic anhydride. The hydrogen sulphate of the "*cis*"-isomer exhibits abnormally low solubility, whereas the solubility of the acetate appears to be normal.

"cis"-cyclo*Hexanol-2-sulphonic Acid*.—This acid has been prepared by the action of hydrogen sulphites on *cyclo*hexene oxide (cf. Lauer and Hill, *J. Amer. Chem. Soc.*, 1936, **58**, 1873; Brunel, *Bull. Soc. chim.*, 1903, [iii], **29**, 884). It can also be prepared by heating 2-chloro*cyclo*hexanol (20 g.) on a steam-bath for 3 days with ammonium sulphate (20 g.) in water (100 ml.). It was isolated as the barium salt (27·0 g., 73%).

Dimer Derivatives.—The barium salts (see above) consisted of approx. equal proportions of the

sulphated hydroxy-sulphonic acid and the olefinic acid. They formed resin-like uncrystallisable salts, readily soluble in both water and alcohol.

In addition to the products described above, a small yield (6.3 g.) of an olefinic acid was obtained. The barium salt formed colourless diamond-shaped plates and gave a benzylthiuronium salt, m. p. and mixed m. p. with the salt of *cyclo*hexene-3-sulphonic acid, 146—147°. Oxidation with nitric acid (conc. acid 2, water 7 parts) at 100° gave succinic acid, but it was not possible to prove that it was actually *cyclo*hexene-3-sulphonic acid so that the possibility remains that it might have been *cyclo*hexene-4-sulphonic acid.

Synthesis of cyclo*Hexene-3-sulphonic Acid.*—3-Bromo*cyclo*hexene [prepared by the action of *N*-bromosuccinimide on *cyclo*hexene (Ziegler *et al.*, *Annalen*, 1942, **551**, 80)], b. p. 75—76°/30 mm., n_D^{20} 1·5142 (Found: Br, 49·1. Calc. for C_6H_9Br: Br, 49·7%) (10·65 g.) was heated on the steam-bath for 4 days with ammonium sulphite (7·7 g.) in water 40 ml., air being excluded by means of nitrogen or carbon dioxide. The product was treated with barium hydroxide, and barium *cyclo*hexene-3-sulphonate was obtained as colourless hexagonal crystals (Found: Ba, 28·65%) (1·2 g.), having the same properties and giving the same derivatives (mixed m. p.) as the salt described above.

1-*Methyl*cyclo*pentene.*

Preparation.—*cyclo*Pentanone was prepared from adipic acid and barium hydroxide (Thorpe and Kon, *Org. Synth.*, Coll. Vol. I) and then treated with methylmagnesium iodide according to Zelinsky and Nametkin (*Ber.*, 1902, **35**, 2683). The product was treated with water and the resulting 1-methyl*cyclo*pentanol dehydrated to 1-methyl*cyclo*pentene by distilling it over anhydrous potassium carbonate. The product was purified by fractionation and then had b. p. 75·5°/752 mm., d_4^{20} 0·7758, n_D^{20} 1·4352, bromine no. 193. It was oxidised by alkaline potassium permanganate at 0° to pentan-4-one-1-carboxylic acid hydrate, m. p. 35—37° (Block and Thomas, *J. Amer. Chem. Soc.*, 1944, **66**, 1589, give m. p. 36—37°).

Sulphonation.—A suspension of dioxan–sulphur trioxide complex in ethylene dichloride was prepared containing 37 g. of sulphur trioxide. To the well stirred mixture, cooled to 0°, a solution of 19·68 g. of 1-methyl*cyclo*pentene in ethylene dichloride was gradually added. Unlike the reaction with *cyclo*hexene, the mixture did not thicken but became clear and fluid after the completion of the reaction (½ hr.). The mixture was then diluted with water, the ethylene dichloride layer separated, the aqueous layer neutralised with barium hydroxide, and the precipitated barium sulphate filtered off. The filtrate was evaporated to small bulk under reduced pressure, and alcohol was added to precipitate the *disulphonates*, which were purified by reprecipitation and gave 13·5 g. of dried material (*A*) (see below). The alcoholic filtrate was evaporated to small bulk under reduced pressure and allowed to crystallise. 37·7 G. of crystals were obtained, which consisted of *barium* 1-*methyl*cyclo*pentene-5-sulphonate*. No sulphated hydroxy-sulphonic acids were present.

The above barium salt crystallises from aqueous alcohol in needles [Found: Ba, 27·63. $(C_6H_9SO_3)_2Ba,2H_2O$ requires Ba, 27·68%]. It loses one molecule of water at 120° but decomposes when heated to 140°. It is readily soluble in water or 90% alcohol, and is not precipitated on addition of excess of alcohol. With alkaline potassium permanganate at 0° it gives succinic acid, m. p. and mixed m. p. 183—184° (Found: equiv., 61·4. Calc. for $C_4H_6O_4$: equiv., 59), and acetic acid (benzylthiuronium salt, elongated rectangular plates, m. p. and mixed m. p. 134—136°) which establishes the constitution of the acid. The aqueous solution of the barium salt readily decolorises bromine water, but no barium sulphate is precipitated.

The benzylthiuronium salt crystallised from 50% aqueous alcohol in needles, m. p. 79—80·5°. The phenylhydrazine derivative was unobtainable owing to decomposition of the acid on the steam-bath.

Action of Sulphuric Acid.—This reaction is of particular interest in that it demonstrates the weakness of the carbon–sulphur bond in 1-methyl*cyclo*pentene-5-sulphonic acid. The dry barium salt of this acid was added slowly to concentrated sulphuric acid at room temperature. A vigorous reaction ensued with evolution of heat and sulphur dioxide. On pouring the mixture into water, a green oil separated which appeared to consist of a mixture of unsaturated polymers.

Barium Disulphonates Insoluble in 75% Alcohol.—The yellow solid (*A*, above) could not be crystallised (Found: Ba, 34·3. $C_6H_8S_2O_6Ba,H_2O$ requires Ba, 34·7%).

Summary of Yields.—The following are total yields, based on the hydrocarbon. (*a*) Barium *cyclo*hexenesulphonate, 40·5; barium "*trans*"-2-sulpho*cyclo*hexyl hydrogen sulphate, 55·4; dimers, 17·3; total, 68·4%. (*b*) Barium 1-methyl*cyclo*pentene-5-sulphonate, 63·4; barium methyl*cyclo*pentene-disulphonates, 14·1; total, 77·5%.

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411. *Reactions of Cyclic Hydrocarbons. Part II. The Polymerisation of cyclo*Hexene *and* 1-*Methylcyclo*pentene.

By R. Sperling.

*cyclo*Hexene is polymerised by 97% sulphuric acid at 0°, the polymerisation being accompanied by change in ring-size and disproportionation, resulting in the formation of two series of polymeric oils, one almost completely saturated and insoluble in the acid layer, and the other consisting of diolefins soluble in the acid layer. The saturated dimeric fraction contains 1-*cyclo*hexyl-2-methyl*cyclo*pentane and 1-*cyclo*hexyl-3-methyl*cyclo*pentane, whereas the unsaturated dimeric fraction appears to contain diolefins derived from *cyclo*hexyl-methyl-*cyclo*pentane.

1-Methyl*cyclo*pentene is dimerised by 87% sulphuric acid, but with 97% acid gives rise to products similar to those from *cyclo*hexene.

The action of sulphuric acid on olefins has received considerable attention since Brookes and Humphrey (*J. Amer. Chem. Soc.*, 1918, **40**, 822) found that the acid polymerises, hydrates, and sulphates olefins. Nametkin and Abakumovskaya (*Ber.*, 1933, **66**, 358) treated *cyclo*hexene with sulphuric acid, and obtained two series of polymers: saturated acid-insoluble and unsaturated acid-soluble. The latter authors found that the former series consisted principally of the dimer and trimer which were completely saturated, and suggested that they were di- and tri-*cyclo*hexyl respectively, but were unable to dehydrogenate them to the corresponding aromatic compounds. *cyclo*Hexene has been polymerised by a number of other reagents, including hydrogen fluoride (McElvain and Langston, *J. Amer. Chem. Soc.*, 1944, **66**, 1759), aluminium chloride (Waterman *et al.*, *Rec. Trav. chim.*, 1935, **54**, 245), boron trichloride (Hoffmann, *Chem. Ztg.*, 1933, **57**, 5), and benzoyl peroxide (Farmer and Michael, *J.*, 1942, 513; Hermans and Van Eyk, *J. Polymer Sci.*, 1946, **1**, 407), but, with the exception of those from aluminium chloride, the products differed from those obtained with sulphuric acid.

Whereas sulphuric acid of concentrations less than 90% sulphates and hydrates *cyclo*hexene at 0°, 97% acid gives, as principal products, two series of polymeric oils, one insoluble in the acid layer and consisting almost entirely of saturated hydrocarbons, and the other soluble in the acid layer and consisting of highly unsaturated reactive polymers. These two series were separated and then fractionated, and the properties of the fractions examined.

The acid-insoluble polymers consisted principally of the dimer and trimer fractions, which were completely saturated. The tetrameric fraction, however, contained approximately 30% of olefinic hydrocarbons. The dimeric fraction could be separated into two components, whose physical properties approximated to those of 1-*cyclo*hexyl-2-methyl*cyclo*pentane (Orchin and Feldman, *J. Amer. Chem. Soc.*, 1946, **68**, 2737), and 1-*cyclo*hexyl-3-methyl*cyclo*pentane (Zelinsky and Titz, *Ber.*, 1925, **58**, *B*, 2755). They resisted dehydrogenation over palladised charcoal at 340°, under which conditions di*cyclo*hexyl readily yields diphenyl, but they were readily dehydrogenated to the corresponding phenylmethyl*cyclo*pentane at 410°.

The unsaturated series of polymers differed from the saturated series in containing only a small amount of dimer, somewhat larger amounts of trimer and tetramer, and an undistillable residue containing polymers of higher molecular weight. The last-named were highly reactive diolefins, but the dimers appeared to be derivatives of *cyclo*hexyl-methyl-*cyclo*pentane. The diolefins reacted vigorously with bromine in carbon tetrachloride by substitution, absorbed atmospheric oxygen, decolorised potassium permanganate, reduced silver nitrate to silver, and ferric to ferrous salts, and formed coloured complexes with mineral acids; they absorbed ultra-violet light very strongly, reacted abnormally with maleic anhydride, and were hydrogenated in the presence of Raney nickel, giving colourless saturated hydrocarbons whose properties approached those of the corresponding saturated polymer. The hydrogenated dimer could be dehydrogenated by palladised charcoal at 410°. In addition, the diolefins reacted with perbenzoic acid, the trimer and tetramer absorbing two atoms of oxygen per molecule. Sulphonation of the diolefins with dioxan–sulphur trioxide complex (Suter *et al.*, *J. Amer. Chem. Soc.*, 1938, **60**, 538) produced a range of sulphonic acids, whose barium salts could be partly separated by addition of alcohol to an aqueous solution. Those salts containing between 3 and 4 sulpho-groups per molecule were readily precipitated, those remaining in solution consisted principally of sulphated hydroxy-sulphonic acids containing one sulpho-group per molecule. They decolorised potassium permanganate and bromine water, but only a trace of barium sulphate was precipitated by the latter reagent.

1-Methyl*cyclo*pentene was dimerised by 87% sulphuric acid at 5° (Bearse and Leonard, U.S.P. 2,419,668). The dimer contained one double bond and was dehydrogenated to phenyl-

methyl*cyclo*pentane by passage over palladised charcoal at 410°, indicating that it consisted of *cyclo*hexenyl-methyl-*cyclo*pentane. Treatment of the dimer with 97% sulphuric acid at 10° gave saturated acid-insoluble and unsaturated acid-soluble polymers. The properties of the mixed saturated dimeric fraction were almost identical with those of the mixed saturated dimeric fraction obtained by the sulphuric acid polymerisation of *cyclo*hexene. Unlike 1-methyl*cyclo*pentene, *cyclo*hexene could not be dimerised by 88% sulphuric acid.

Experimental.

(B. p.s are corrected.)

cyclo*Hexene*.

Preparation and Separation of the Two Series of Polymers.—*cyclo*Hexene (300 g.) was added slowly during 5 hours to 97% sulphuric acid (750 g.), the reaction temperature being maintained at 0°. The mixture was then stirred for a further hour, being kept blanketed all the time by a current of purified nitrogen. As the reaction proceeded, the acid layer became orange in colour but no sulphur dioxide was evolved. After the reaction, the mixture was blanketed with carbon dioxide and set aside overnight in the refrigerator at −25°. The lower, acid layer was then separated from a pale yellow oil (110 g.), containing the saturated series of polymers.

To the lower, acid layer was added an equal weight of ice while the mixture was cooled in a freezing mixture. A greenish viscous oil was precipitated and was extracted with light petroleum (b. p. 40—60°) and then washed free from acid with sodium sulphate solution, the colour changing from bluish- to brownish-green and finally to light orange at complete neutrality. The light petroleum was then removed under reduced pressure. The residual viscous oil (155 g.) contained the unsaturated polymers. In processing the unsaturated polymers, care must be taken to exclude oxygen by blanketing with nitrogen or carbon dioxide.

Distillation of Saturated Polymers.—91 G. of the saturated polymeric oils were distilled at 4 mm. and fractionated through a 3-ft. column, 1 inch in diameter, packed with glass helices, and equivalent to 15 theoretical plates. The following fractions were obtained: (i) b. p. 73—79°/4 mm. (26·04 g., 28·6%), dimer; (ii) b. p. 138—146°/4 mm. (10·36 g., 11·4%), mixed dimer–trimer; (iii) b. p. 146—148°/4 mm. (25·25 g., 27·7%) trimer; (iv) b. p. 148—192°/4 mm. (8·93 g., 9·8%), mainly trimer; (v) b. p. 255—265°/15 mm. (4·89 g., 5·4%), a pale yellow viscous oil, tetramer; and a residue (10·0 g., 11·0%), a light-brown very viscous oil. Fractions (i)—(iv) were colourless, odourless oils. See also Table I.

Table I.

Saturated series of polymers.	Mixed dimer.	Trimer.	Tetramer.
n_D^{20}	1·4749	1·4965	1·5088
d_4^{20}	0·8771	0·9189	0·9360
Molecular weight	165	249·5	335
Aniline point	49·5°	69·0°	82·9°
Bromine no.	0	0	14·5
Carbon, found	86·04%	86·24%	—
Hydrogen, found	12·96%	12·63%	—
Unsaturated series of polymers.	**Dimer.**	**Trimer.**	**Tetramer**
n_D^{20}	1·5011	1·5200	1·5287
d_4^{20}	0·9173	0·94607	0·96423
Molecular weight	161·5	245	330
Aniline point	—	33·2°	46·0°
Bromine no. (I.P. Method)	77·6	−10·3	−8·1
Total Br/100 g.	200	180·3	153·2
HBr/100 g.	62·5	96·1	81·6
Bromine no. (Wijs)	—	182	155·0
Bromine no. (A.S.T.M.)	—	110·5	93·8
Carbon, found	86·85%	87·00%	87·04%
Hydrogen, „	11·35%	11·57%	1·24%
Sulphur, „	1·635%	0·97%	0·51%

Carbon and hydrogen contents were determined by Drs. Weiler and Strauss, Oxford.

Distillation of Unsaturated Polymers.—140 G. of the unsaturated polymers were distilled at 3 mm. to give the following fractions: (i) b. p. 60—121°/3 mm. (14·32 g., 9·9%), mixed dimer–trimer; (ii) b. p. 126—136°/3 mm. (30·11 g., 20·8%), trimer; (iii) b. p. 168—178°/3 mm. (7·17 g., 5·0%), mixed trimer–tetramer; (iv) b. p. 182—200°/3 mm. (23·60 g., 16·3%), tetramer; residue (62·0 g., 42·7%), a brown resin. Fractions (i)—(iv) were yellow oils of terpinic odour. See also Table I.

The preparation of the polymeric oils was repeated by treating 450 g. of peroxide-free *cyclo*hexene with 1125 g. of 97% sulphuric acid at 0° and yielded 140 g. of saturated polymers and 285 g. of unsaturated polymers. The distillates obtained were similar to those from the first preparation except that the saturated dimer could be separated into two fractions, and that approx. 9% of an unsaturated dimer could be obtained from the unsaturated polymers. Two dimeric fractions were obtained: b. p. 224·5—225°/760 mm., d_4^{20} 0·8712, n_D^{20} 1·4719, aniline point 48°; b. p. 231—232°/760 mm., d_4^{20} 0·8793, n_D^{20} 1·4760, aniline point 48·5°.

Reactions of Saturated Series.—Dehydrogenation. (i) *Palladised charcoal.* The method employed was based on that of Zelinsky (*Ber.*, 1924, **57**, 150; 1926, **59**, 2580). 1 G. of oil was vapourised per hour in a current of carbon dioxide and passed over heated 10% palladised charcoal. The dehydrogenated product was condensed, the carbon dioxide was absorbed in alkali, and the hydrogen formed was collected and measured. The amount of dehydrogenation was determined by ascertaining the change in physical properties and by the hydrogen evolved. The amount of undehydrogenated matter in the product could be measured by noting the volume of residual oil on treatment with 20% oleum.

Di*cyclo*hexyl was readily dehydrogenated to diphenyl at 340°, whereas 1-*cyclo*hexyl-2-methyl*cyclo*pentane, a sample of which was kindly supplied by Dr. M. Orchin, U.S. Bureau of Mines, was dehydrogenated at 410° giving, in a single pass, 79% of 1-phenyl-2-methyl*cyclo*pentane and 21% of residual 1-*cyclo*hexyl-2-methyl*cyclo*pentane. This mixture solidified on cooling in solid carbon dioxide–alcohol and melted sharply on rewarming, whereas a 3 : 1 mixture of diphenyl and 1-*cyclo*hexyl-2-methyl*cyclo*pentane melted at 55°. The 1-phenyl-2-methyl*cyclo*pentane was readily absorbed by 20% oleum.

The changes in physical properties of the dimeric hydrocarbons obtained by dehydrogenation are described in Table II.

TABLE II.

	B. p.	d_4^{20}.	n_D^{20}.	Aniline point.	Vol. (%) insoluble in oleum.
1-*cyclo*Hexyl-2-methyl*cyclo*pentane	222·4°/ 760 mm.	0·8683	1·4705	—	—
do. after dehydrogenation *	—	0·91325	1·5167	13·6°	38·0
*cyclo*Hexene saturated dimer, fraction (i)	224·5—225°/ 760 mm.	0·8712	1·4719	48·0	—
do. after dehydrogenation *	—	0·9257	1·5277	−12·0	21·0
*cyclo*Hexene saturated dimer, fraction (ii)	231—232°/ 760 mm.	0·8793	1·4760	48·5	—
do. after dehydrogenation *	—	0·9185	1·5168	7·0	25·0
Hydrogenated *cyclo*hexene unsaturated dimer	—	—	1·4855	—	—
do. after dehydrogenation *	—	—	1·5080	—	—
1-Methyl*cyclo*pentene dimer (hydrogenated)	224—229°/ 752 mm.	0·8790	1·4798	46·0	—
do. after dehydrogenation *	—	0·9230	1·5253	−10·0	22·0
1-Phenyl-2-methyl*cyclo*pentane (by extrapolation)	—	0·941	1·5430	< −20	—

* The substance was passed over the catalyst once only.

(ii) *Nickel chromite.* 2·1 G. of saturated dimer in 20 ml. of benzene were heated with 2 g. of reduced nickel chromite at 250° for 5 hours under nitrogen, the charging pressure being 50 atmospheres, according to the method described by McElvain and Langston (*J. Amer. Chem. Soc.*, 1944, **66**, 1759) and by Adkins *et al.* (*ibid.*, 1941, **63**, 1320). The dimer was unchanged.

Reactions of Unsaturated Series.—(a) *Reaction with bromine.* The bromine numbers determined by the I.P. method ("Standard Methods for Testing Petroleum and its Products," p. 46, Institute of Petroleum, 1948) were unsatisfactory as the reaction appeared to proceed predominantly by substitution. With Wijs's reagent, a solution of iodine monochloride in acetic acid, the reaction appeared to proceed to the same extent as with bromine in carbon tetrachloride. More satisfactory results were obtained with the A.S.T.M. Method ("A.S.T.M. Standards on Petroleum Products and Lubricants," p. 328, American Society for Testing Materials, 1946) in which a mixed potassium iodide–iodate reagent is used, approx. 4 atoms of halogen reacting per molecule of unsaturated polymer.

5·94 G. of unsaturated tetramer were dissolved in 50 ml. of dry carbon tetrachloride, and the solution was cooled to −10°. 12 G. of bromine in 50 ml. of carbon tetrachloride were run in rapidly with stirring, the temperature being maintained at −10°. The product was washed with aqueous sodium hydrogen sulphite, followed by water, and finally shaken with calcium carbonate until free from mineral acid. The carbon tetrachloride layer was separated, dried (Na_2SO_4), and filtered, and the bulk of the solvent removed under reduced pressure. The product was a golden-brown resinous oil which decomposed when kept or heated, evolving hydrogen bromide and changing in colour to dark green. The carbon tetrachloride could not be completely removed without decomposition of the product. The product contained 14·65% of carbon tetrachloride and the bromine content of the brominated tetramer was 37·0% (after correction for carbon tetrachloride present); the molecular weight (cryoscopic in benzene) was 524. The bromine content corresponded to the addition of 3·2 atoms of bromine per tetramer molecule, the calculated molecular weight of the tribromide being 590. When the product was heated on the steam-bath for several hours, the colour changed to dark olive-green and a hard resin resulted, having bromine content, 28·84%, *M*, 719, indicating that it was formed by condensation of two molecules of brominated tetramer with the loss of four atoms of bromine.

(b) *Oxidation.* (i) *Atmospheric.* 0·8643 G. of unsaturated tetramer was placed in a 100-ml. CO_2 flask open to the air. The oil gradually darkened and increased in weight by 0·0639 g. in 63 days. The product was then treated with light petroleum to precipitate asphaltic matter (0·103 g.). The increase in weight corresponds to an addition of 1½—2 atoms of oxygen per tetramer molecule. The oxidised oil had molecular weight (cryoscopic in benzene) of 382 (calc. for addition of 2O : 360). Though the oil liberated iodine from potassium iodide after exposure to the atmosphere for a few days, it did not do so after 63 days.

(ii) *Perbenzoic acid.* A 0·178N- solution of perbenzoic acid in chloroform was prepared by treating benzoyl peroxide with sodium methoxide at 0°. 20 Ml. of the solution were added to a weighed sample of the unsaturated polymer in a stoppered glass bottle and maintained for 48 hours at −20°, light being excluded. A blank determination was also carried out. After the reaction, the residual perbenzoic acid was determined by potassium iodide, and the liberated iodine titrated. Results were:

	Unsaturated dimer.	Unsaturated trimer.	Unsaturated tetramer.
Wt. of sample, g.	0·1108	0·1163	0·2064
0·1N-Thiosulphate, ml.	19·75	19·85	24·65
Oxygen absorbed, g./mol.	23·1	33·4	32·0

(iii) *Potassium permanganate.* Unsaturated dimer (1·1 g.) was treated with a dilute solution of potassium permanganate in 1% aqueous sodium carbonate at 0°. No organic matter could be extracted from the product after acidification.

(iv) *Nitric acid.* Unsaturated dimer (1 g.) reacted with nitric acid (*d* 1·28) at 80°; 0·0994 g. of fatty acid (equiv., 261·5) was obtained.

(v) *Alcoholic silver nitrate.* Unsaturated trimer (1·4988 g.) was heated under reflux with excess of alcoholic silver nitrate for 1 hour under carbon dioxide. A silver mirror was produced, with 0·8705 g. of a grey precipitate containing 95·5% of silver.

(vi) *Ferric chloride.* A few drops of the unsaturated trimer were shaken with an aqueous solution of ferric chloride and potassium ferricyanide. A deep-blue colour and precipitate were formed, whilst a blank sample of reagent itself remained unchanged.

(c) *Hydrogenation.* Before dehydrogenation, the unsaturated dimer was subjected to desulphurisation by heating its alcoholic solution under reflux for 4 hours with 20 g. of Raney nickel (Mozingo *et al.*, *J. Amer. Chem. Soc.*, 1943, **65**, 1013). After removal of the solvent, the sulphur content was almost unchanged (1·615%). The "desulphurised oil" (5 g.) in ethyl alcohol (30 ml.) was hydrogenated with Raney nickel (5 g.) for 3 hours at 160° with a hydrogen pressure of 1500 lb./sq. in. The product, after removal of solvent and catalyst, was a pale yellow oil which still reacted with bromine by substitution (15·9 g. of bromine per 100 g.; 7·5 g. of HBr evolved per 100 g.). The oil was shaken with an excess of concentrated sulphuric acid, and the acid-insoluble oil was washed with water, treated with a little absorbent clay, and filtered. The purified oil was saturated and colourless. The unsaturated trimer and tetramer were hydrogenated by the same procedure. The properties of the hydrogenated products were:

	Dimer.	Trimer.	Tetramer.
d_4^{20}	—	0·9281	0·952
n_D^{20}	1·4855	1·4998	1·5125
Aniline point	—	59·6°	58·0°

(d) *Dehydrogenation.* (i) *Selenium.* The unsaturated dimer (4·102 g.) and selenium (9·8 g.) were heated at 270° for 20 hours, after which the temperature was raised to 330°. 1·1559 G. of hydrogen selenide were collected in absorption tubes. The product was purified by extraction with benzene and redistillation over sodium. The product was an oil which gave no picrate, nitro-, or aroylbenzoic acid derivative. The amount of hydrogen selenide produced was only 10% of that required for complete dehydrogenation of the naphthenic to aromatic rings. Similar results were obtained with the unsaturated trimer.

(ii) *Palladised charcoal.* When passed over palladised charcoal at 410°, the hydrogenated unsaturated dimer was partly dehydrogenated. Little of the sample was available, but the change in *n* was determined (see Table II).

(e) *Ultra-violet light absorption.* There was a broad maximum with its centre at 2512·5 A. ($E_{1\text{ cm.}}^{1\%}$ 5000). The absorption decreased at shorter wave-lengths with a minimum at 2325 A. ($E_{1\text{ cm.}}^{1\%}$ 4350). The intensity of absorption indicates the presence of conjugated double bonds, but is not a reliable guide to the number of double bonds present.

(f) *Reaction with maleic anhydride.* The unsaturated trimer (1·488 g.) in benzene (5 ml.) was heated with maleic anhydride (2·0 g.) in a sealed tube for 24 hours at 100°. After removal of the benzene and residual maleic anhydride, the adduct was hydrolysed and isolated as a water-insoluble fatty acid. After purification, the product was a pale yellow resin having an equivalent weight of 299. The molecular weight of the dicarboxylic acid would thus be 598, which indicates the reaction of two molecules of trimer with one of maleic anhydride. The acid was soluble in light petroleum and insoluble in water, decolorised potassium permanganate, and reacted with 74 g. of bromine per 100 g. The residual oil (42%) had n_D^{20} 1·5142, and reacted with 74 g. of bromine per 100 g. The acid was converted into the barium salt (Found: Ba, 16·6; *M*, 826·5. Calc.: Ba, 18·5%); *M*, 741).

The unsaturated tetramer (1·9492 g.) was similarly treated with maleic anhydride (4 g.). The resulting carboxylic acid had a molecular weight of 684 (calc. for reaction of two molecules of tetramer with one of maleic anhydride, 776). The acid reacted with 40·5 g. bromine per 100 g. The residual oil (52%) had n_D^{20} 1·5270, reacted with 108·5 g. of bromine per 100 g., and gave a barium salt (Found: Ba, 14·0%; *M*, 979·5. Calc.: *M*, 911).

(g) *Sulphonation.* (i) *Unsaturated* cyclo*hexene trimer.* This trimer (5·13 g.) was treated with an excess of dioxan–sulphur trioxide complex in ethylene dichloride at 0°. Only a trace of sulphur dioxide was produced, and the product, after dilution and removal of neutral oils, etc., was neutralized with barium hydroxide. The resulting water-soluble barium salts were separated into three fractions by addition of alcohol to the aqueous solution.

Fraction (1) (3·04 g.) was insoluble in 50% alcohol, being precipitated as a viscous oil. The barium content (31·0%) was equivalent to 3·3 sulpho-groups per trimer molecule. It formed uncrystallisable

dark brown resins, reduced potassium permanganate, and decolorised bromine water although only a trace of barium sulphate was precipitated. The derived benzylthiuronium derivative was a brown oil which could not be crystallised. The sulphonic acids did not contain any sulphated hydroxy-compounds.

Fraction (2) (1·55 g.) was soluble in 50% alcohol but insoluble in 90% alcohol. The barium content (29·0%) was equivalent to 3·0 sulpho-groups per trimer molecule. The properties were similar to those of fraction (1), but the product was lighter in colour and contained a small percentage of sulphated hydroxy-sulphonic acids.

Fraction (3) (1·32 g.) remained in solution after addition of excess of alcohol to the aqueous solution. The barium content was 24·46%. Hydrolysis showed that these salts were principally sulphated hydroxy-sulphonates containing one sulphated hydroxy-sulphonic acid group per trimer molecule. They were unsaturated and gave oily benzylthiuronium derivatives.

(ii) *Unsaturated* cyclo*hexene tetramer*. This tetramer fraction (3·23 g.) was sulphonated by means of the dioxan–sulphur trioxide complex in a similar manner to the trimer, the barium salts of the resulting sulphonic acids being separated by addition of alcohol to an aqueous solution.

Fraction (1) (1·12 g.), insoluble in 50% alcohol, had a barium content (29·54%) equivalent to four sulpho-groups per tetramer molecule. The properties were similar to those of the corresponding trimer products. Fraction (2) (0·62 g.) had a barium content (28·48%) equivalent to 3·7 sulpho-groups per tetramer molecule. Fraction (3) (0·71 g.) had a barium content of 26·5%. It contained a large proportion of sulphated hydroxy-sulphonic acids, in addition to some polysulphonic acids.

1-*Methyl*cyclo*pentene*.

1-*Methyl*cyclo*pentene Dimer*.—A sample was kindly supplied by Dr. A. E. Bearse, Battelle Memorial Institute, Columbus, Ohio, U.S.A., who prepared it by treating 1-methyl*cyclo*pentene with 87% sulphuric acid at 5° (Bearse and Leonard, U.S.P. 2,419,668). It had b. p. 126—128°/50 mm. d_4^{20} 0·914, n_D^{20} 1·4962, Br no. (I.P. method), 43 g. per 100 g. (substitution, 62 g. of bromine per 100 g.) or (A.S.T.M. method) 111 g. per 100 g. (Calc.: 97·6) (Found: C, 87·2; H, 12·1. Calc. for $C_{12}H_{20}$: C, 87·8; H, 12·2%). After dehydrogenation, the Br no. (A.S.T.M.) was 3·7, indicating that the double bond is present in the *cyclo*hexane and not in the *cyclo*pentane ring.

Hydrogenation.—A solution of the dimer in *cyclo*hexane was hydrogenated for 22 hours at 160°/2500 lbs. per sq. in. The product, treated with sulphuric acid, freed from acid, and distilled, had b. p. 224—229°/752 mm., d_4^{20} 0·8790, n_D^{20} 1·4798, and aniline point 46·0.

Treatment with Sulphuric Acid.—The unsaturated dimer was shaken with an excess of 97% sulphuric acid at 10°, and the acid-insoluble polymers were collected, freed from acid, and distilled; the dimer fraction had b. p. 223—226°/758 mm., d_4^{20} 0·8788, n_D^{20} 1·4774, and aniline point 46·9°. The dimer did not solidify in solid carbon dioxide–alcohol.

The author thanks Dr. R. Schnurmann and Mr. W. F. Maddams, Physics Department, Manchester Oil Refinery Ltd., for determining the ultra-violet light absorption spectra recorded in this and the succeeding paper, and Mr. I. Goodman, Petrocarbon Ltd., for his assistance in dehydrogenating naphthenes.

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412. *Reactions of Cyclic Hydrocarbons. Part III. The Action of Oleum on* cyclo*Hexane,* cyclo*Hexene, and Related Hydrocarbons.*

By R. SPERLING.

All the *cyclo*alkanes examined (*cyclo*hexane, di*cyclo*hexyl, *cyclo*hexyl-methyl-*cyclo*pentane, and decahydronaphthalene) are attacked only slowly by oleum at moderately low temperatures. Oleum appears to dehydrogenate these hydrocarbons to unsaturated compounds which are then polymerised, the resulting unsaturated polymers being subsequently oxidised and sulphonated. Only a small proportion of the *cyclo*alkane is completely dehydrogenated to the corresponding aromatic compound, *cyclo*hexane giving a small yield of benzenesulphonic acid, and decahydronaphthalene a small proportion of naphthalene-2-sulphonic acid. Neither tetrahydronaphthalene nor its sulphonation products are formed as intermediate compounds during the latter reaction.

Oleum and *cyclo*hexene give rise to unsaturated polymers and their oxidation and sulphonation products, together with products resulting from the primary sulphonation of *cyclo*hexene, modification by the excess of oleum present also occurring. In addition, *cyclo*hexyl hydrogen sulphate is produced under mild conditions, and a little benzenesulphonic acid under severer conditions.

ALTHOUGH earlier workers (Orndoff and Young, *Amer. Chem. J.*, 1893, **15**, 261; Worstall, *ibid.*, 1898, **20**, 664; Markownikow, *Annalen*, 1905, **341**, 131; and Menchutkin and Wolf, *Neft Khoz.*, 1927, **13**, 340) showed that alkanes and *cyclo*alkanes were attacked by oleum, the resulting sulphonation products were not extensively investigated until Burkhardt (*J.*, 1930, **133**, 2387) examined the action of oleum on hexane, *cyclo*hexane, and methyl*cyclo*hexane, and showed that *cyclo*hexane gave only a small yield of benzenesulphonic acid and that a large

proportion of the reaction products consisted of mixed sulphonic acids of unknown composition, their analyses indicating that they consisted of mono- and di-sulphonic acids together with a considerable proportion of sulphated hydroxy-sulphonic acids.

It has now been shown that *cyclo*hexane reacts slowly at 10° with excess of oleum containing approximately 20% of sulphur trioxide, rather more than 1 mole of sulphur dioxide being produced per mole of *cyclo*hexane attacked. The principal products are sulphonic acids and hydrogen sulphates derived from unsaturated polymeric compounds, and they resemble closely those produced by sulphonating the unsaturated polymers derived from *cyclo*hexene (cf. Part II, preceding paper). A small yield (less than 2%) of benzenesulphonic acid is also obtained, together with residual partly oxidised unsaturated polymeric compounds. With oleum containing approximately 60% of sulphur trioxide, *cyclo*hexane is attacked slowly but somewhat more extensively, the products being similar to those produced with oleum containing 20% of sulphur trioxide except that the sulphonic acids and hydrogen sulphates derived from the unsaturated polymers appear to be more strongly oxidised.

Unlike *cyclo*hexane, *cyclo*hexene is readily attacked by oleum, the resulting products varying according to the conditions employed. Under mild conditions the principal products are *cyclo*hexyl hydrogen sulphate and the unsaturated polymeric oils. Accompanying them are products resulting from the primary sulphonation of *cyclo*hexene, viz., *cyclo*hexene-3-sulphonic acid, a sulphated hydroxy-sulphonic acid which has been modified by either dehydrogenation or isomerisation, and olefin-disulphonic acids, probably including *cyclo*hexene-3 : 6-disulphonic acid. Under more severe conditions, products resulting from the oxidation and sulphonation of the unsaturated polymeric oils appear, while *cyclo*hexyl hydrogen sulphate is not found. The products formed under these more severe conditions closely resemble those formed from *cyclo*hexane by oleum, and include a small amount of benzenesulphonic acid. With oleum containing approximately 60% of sulphur trioxide, the reaction is so vigorous as to be uncontrollable.

Both di*cyclo*hexyl and *cyclo*hexylmethyl*cyclo*pentane resemble *cyclo*hexane in being but slowly attacked by oleum, giving rise to a mixture of sulphonic acids and hydrogen sulphates derived from unsaturated polymeric compounds.

Decahydronaphthalene is also slowly attacked by oleum, the products being principally oxidation and sulphonation products derived from unsaturated polymeric compounds. Approximately two moles of sulphur dioxide are evolved during the reaction, and the properties of the residual unattacked decahydronaphthalene suggest that the *cis*-decahydronaphthalene is preferentially attacked. A small amount of naphthalene-2-sulphonic acid is also produced, but no tetrahydronaphthalenesulphonic acid; and, as it has been shown that excess of oleum does not dehydrogenate tetrahydronaphthalene or its sulphonation products, it is unlikely that these substances are produced as intermediate compounds during the action of oleum on decahydronaphthalene.

Discussion.—The reaction of oleum with *cyclo*hexane is probably initiated by the removal of a hydrogen atom by sulphur trioxide, acting as an oxidizing agent, to give a *cyclo*hexyl radical which could then either react with sulphur trioxide, ultimately to form *cyclo*hexanesulphonic acid, or be further dehydrogenated to *cyclo*hexene. The amount of sulphur dioxide evolved indicates, on the average, the removal of two hydrogen atoms per molecule of *cyclo*hexane reacting. If *cyclo*hexanesulphonic acid were produced by the action of sulphur trioxide on *cyclo*hexane, it would be unstable in the presence of oleum and would be further dehydrogenated to give *cyclo*hexene and polymeric sulphonic acid as well as some benzenesulphonic acid. The fact that a larger amount of benzenesulphonic acid (*ca.* 17·5%) is produced by the action of oleum on *cyclo*hexanesulphonic acid than on *cyclo*hexane is an indication that *cyclo*hexanesulphonic acid is not a principal intermediate reaction product, but that further dehydrogenation of the *cyclo*hexyl radical occurs to give *cyclo*hexene, which then reacts with oleum.

*cyclo*Hexene forms *cyclo*hexyl hydrogen sulphate by the polar addition of sulphuric acid. It also polymerises in the presence of sulphuric acid, giving rise to two series of polymers which have been described in Part II (*loc. cit.*). In the presence of sulphur trioxide, the polymerisation of *cyclo*hexane appears to undergo modification, in that the formation of the saturated series of polymers is completely suppressed, while the unsaturated polymers tend to oxidise and sulphate. This would indicate that the sulphur trioxide intercepts the hydrogen atoms being transferred in disproportionation and reacts with them to form sulphur dioxide and water. It is thought that the saturated polymers are not formed first and then removed by reaction with oleum, as the reaction of the saturated polymers with oleum proceeds very slowly. The presence of sulphur trioxide would not interfere with the formation of the

unsaturated series of polymers, and these would react with sulphur trioxide forming a complex mixture of mono-, poly-, and anhydro-sulphated hydroxy-sulphonic acids (cf. Part II). Although the properties of the oxidised and sulphonated unsaturated polymeric compounds produced by the action of excess of oleum on *cyclo*hexene resemble those of the products from *cyclo*hexane, it was not possible to show that they were identical as they did not yield satisfactory derivatives.

*cyclo*Hexene reacts with sulphur trioxide to form *cyclo*hexene-3-sulphonic acid and anhydro-2-sulpho*cyclo*hexyl hydrogen sulphate (cf. Part I, this vol., p. 1925). In the presence of excess of sulphur trioxide, the formation of *cyclo*hexene-3 : 6-disulphonic acid is possible. *cyclo*Hexene-3-sulphonic acid is present among the products of the action of oleum on *cyclo*hexene. A sulphated hydroxy-sulphonic acid is also produced, but it is not the expected 2-sulpho-*cyclo*hexyl hydrogen sulphate, but may be either its dehydrogenation or isomerisation product. That it is the dehydrogenation product, *i.e.*, a derivative of *o*-phenolsulphonic acid, is less likely as this would decompose during hydrolysis because of its instability in hot acid. Isomerisation has probably occurred from a six- to a five-membered ring, but it has not been possible to prove this. Similarly, it was not possible to establish the constitution of the unsaturated disulphonic acids produced by the action of oleum on *cyclo*hexene.

Experimental.

(M. p.s and b. p.s are corrected.)

cyclo*Hexane*.—May and Baker's pure *cyclo*hexane was further purified by recrystallisation until a maximum m. p. of 5·5° was attained. The ultra-violet absorption spectrum showed that the purified material contained 0·2% of benzene. The material had d_4^{20} 0·777, n_D^{20} 1·4260, and b. p. 81—81·5°.

cyclo*Hexene*.—This was prepared by dehydrating redistilled *cyclo*hexanol with sulphuric acid (Brunel, *Bull. Soc. chim.*, 1905, **33**, 207). After redistillation several times over sodium, the fraction boiling between 81·75° and 83·75° was collected. Its ultra-violet absorption spectrum showed that no benzene or other aromatic compounds were present. It had d_4^{20} 0·8100 and n_D^{20} 1·4465.

Reaction with Oleum.—The procedure for treating *cyclo*hexane with oleum and for separating and examining the products was practically identical with that used for *cyclo*hexene. In the case of *cyclo*hexane, however, the products were practically all polymeric.

The hydrocarbon was added to the vigorously stirred oleum maintained at the reaction temperature by means of a cooling mixture. A slow stream of purified nitrogen was passed through the apparatus and then through alkali. After completion of the reaction, the reaction mixture was diluted with water, the temperature being kept below 20°. A considerable proportion of the sulphur dioxide was evolved only after dilution. There were two alternative methods of separating the sulphonation products:

(*a*) The diluted acid layer was neutralised with sodium hydroxide solution, the mixture being cooled, and the polymeric oils were then extracted with chloroform. Sodium sulphate was removed from the de-oiled product by careful addition of alcohol. When large amounts of polymeric polysulphonic acids were present, difficulty was experienced in separating them completely from sodium sulphate. The sodium salts of the sulphonation products could then be partly separated by means of 75% aqueous acetone, the disulphonates and polymeric polysulphonates, together with a large proportion of the sulphated hydroxysulphonates, being precipitated as an oily layer. The sodium salts were unsuitable for further separation.

(*b*) The diluted acid layer was neutralised with barium hydroxide, and the precipitated barium sulphate removed by filtration. Neutralisation with barium hydroxide had the disadvantage that the polymeric oils could not be extracted, as they were adsorbed by the precipitated barium sulphate together with a proportion of those sulphonates derived from the polymer oils. The aqueous filtrate was evaporated to dryness under reduced pressure, care being taken that the temperature did not exceed 60°. The dried residue was redissolved in a little warm water and filtered from precipitated barium sulphate. When the *cyclo*hexyl hydrogen sulphate content was high, it was advisable at this stage to recrystallise from water to remove the bulk of the barium *cyclo*hexyl sulphate before attempting to separate the sulphonates which were then found in the mother-liquor. Three volumes of alcohol were added to the filtrate, whereupon the disulphonates, polymeric polysulphonates, and a proportion of the sulphated hydroxy-sulphonates were precipitated as a pale yellow viscous oil, leaving in solution the barium salts of *cyclo*hexyl hydrogen sulphate, the monosulphonic acids, and all of the mono- and some of the poly-sulphonic acids derived from the polymeric oils.

The barium salts separated according to the above method were suitable for analysis as follows. The alcohol-soluble and -insoluble portions having been separated, they were heated in water for at least 4 hours at 120°, thus hydrolysing the sulphated compounds; the hydrolysed mixture was then neutralised with aqueous barium hydroxide, the precipitated barium sulphate was removed by filtration, and the salts were dried to constant weight at 120°.

In the case of those salts precipitated by alcohol, the sulphated hydroxy-sulphonic acids were hydrolysed to the more stable hydroxy-sulphonic acids which could then be separated from the polysulphonic acids by addition of alcohol, only the polysulphonic acids being precipitated.

In the case of the salts which were not precipitated by alcohol, the barium *cyclo*hexyl sulphate was completely removed and the polymeric hydrogen sulphates were hydrolysed, the resulting alcohols being adsorbed by the precipitated barium sulphate. The sulphated hydroxy-sulphonic acids were converted into the corresponding hydroxy-sulphonic acids. The products obtained by hydrolysing

this mixture of salts could be further separated by heating under reflux with a mixture of equal parts of acetic acid and anhydride, whereupon the hydroxy-sulphonic acids were acetylated and dissolved, together with unchanged olefin and polymeric monosulphonic acids, while barium benzenesulphonate remained insoluble.

The various types of sulphonic acids present in the mixture could be estimated by determining the acidity produced on hydrolysis, the increase in weight on acetylation, and elemental analysis. Though the presence of polymer acids prevented the separation of the various acids in a crystalline form (Buckley, *Proc. Manchester Lit. Phil. Soc.*, 1939, **83**, 31), crystalline derivatives could be obtained whose melting points were, however, affected to a greater or smaller extent by contamination with the corresponding polymer derivatives, which could be reduced considerably by treatment with charcoal. The benzyl thiuronium (Chambers and Watt, *J. Org. Chem.*, 1941, **6**, 376) and phenylhydrazine salts (Latimer and Bost, *J. Amer. Chem. Soc.*, 1937, **59**, 2500) were the most suitable; amine salts (Dermer and Dermer, *J. Org. Chem.*, 1942, **7**, 581), however, could not be readily crystallised, nor are the sulphonyl chlorides and sulphonamides recommended, since they were difficult to crystallise in the presence of polymeric derivatives which were themselves sensitive to heat and to phosphorus and hydrogen halides.

Both sets of barium salts, those precipitated and those not precipitated by alcohol, contained unsaturated sulphonic acids, although the more drastic the oleum treatment the more saturated were the resulting sulphonic acids. Treatment of the unsaturated acids with bromine water precipitated only a trace of barium sulphate. Oxidation with nitric acid gave oxalic but no adipic acid, indicating the absence of 1 : 2-derivatives of *cyclo*hexene. Treatment with Raney nickel (Popa, Schwenk, and Whiteman, *J. Org. Chem.*, 1942, **7**, 587) or hydrolysis with dilute hydrochloric acid at high temperatures failed to reveal aromatic sulphonic acids other than benzenesulphonic acid.

Reactions.—cyclo*Hexane*. *cyclo*Hexane (12·5 g.) was treated with oleum (225 g.) containing approx. 20% of sulphur trioxide at 10°. After 2½ hours, 1·85 g. of unchanged *cyclo*hexane remained.

With 200 g. of oleum containing approx. 60% of sulphur trioxide, 22·7 g. of *cyclo*hexane had reacted after 2½ hours at 10°.

cyclo*Hexene*.—When 60 g. of *cyclo*hexene were added slowly to 100 g. of oleum containing approx. 20% of sulphur trioxide, the temperature being maintained at 0°, a vigorous reaction occurred with evolution of sulphur dioxide. The principal products were polymeric oils and *cyclo*hexyl hydrogen sulphate. The former did not contain saturated polymers; the unsaturated polymers were partly oxidized, a small proportion being insoluble in light petroleum. Small amounts of sulphur compounds were also present. The sulphonic acids present included mono- and di-sulphonic acid derivatives of *cyclo*olefins together with sulphated hydroxy-sulphonic acids. At a higher temperature, the yield of polymeric oils increased at the expense of the *cyclo*hexyl hydrogen sulphate. Similarly, increase of the ratio of oleum to *cyclo*hexene increased the yield of the polymeric oils. With yet more drastic conditions, *e.g.*, adding 25 g. of *cyclo*hexene to 300 g. of oleum at 0°, the polysulphonic acid derivatives of the unsaturated polymeric oils became the principal products, while the yield of polymer oils fell off, and the latter showed evidence of increased oxidation. There was an increase in the yield of the monomeric sulphonic acids, that of benzenesulphonic acid becoming approx. 5%. The amount of sulphur dioxide evolved during these reactions varied between 0·1 mole per mole of *cyclo*hexene under mild conditions and 0·5 mole under more severe conditions.

When the sulphur trioxide content of the oleum was increased to approx. 60%, the reaction became uncontrollable.

The action of oleum on *cyclo*hexane and *cyclo*hexene is summarised in the accompanying tables.

The products described below are those obtained by the action of oleum on *cyclo*hexane and *cyclo*hexene under various treatment conditions.

cyclo*Hexyl Hydrogen Sulphate*.—The barium salt could be obtained as the dihydrate, in the form of octagonal plates, by recrystallisation from aqueous alcohol or water (Found: Ba, 25·86. Calc. for $C_{12}H_{22}O_8S_2Ba$: Ba, 25·81%). The benzylthiuronium salt (needles) had m. p. 169° unchanged by admixture with an authentic specimen. Oxidation with nitric acid (*d*, 1·28) at 80° gave adipic acid, m. p. 151°. Methyl*cyclo*pentyl hydrogen sulphate was not present. Heating the aqueous solution for 4 hours at 120° resulted in complete hydrolysis of the barium *cyclo*hexyl sulphate.

Benzenesulphonic Acid.—This was separated as the barium salt but could not be obtained in a pure crystalline form owing to contamination with traces of polymeric sulphonates which inhibited crystallisation. The benzylthiuronium salt was obtained as characteristic hexagonal plates, m. p. 147—148° alone or mixed with an authentic specimen.

Monosulphonic Acids (*Monomeric*).—The barium salts were soluble in 75% aqueous alcohol. They were obtained as a colourless microcrystalline powder, which appeared to consist of clusters of needles (Found: Ba, 28·74%). They were stable to heat up to 220° and to hydrolysis by dilute mineral acids up to 160°, above which temperature decomposition occurred, accompanied by formation of carbon. They decolorised potassium permanganate and bromine water, the latter reagent precipitating no more than a trace of barium sulphate. Oxidation with nitric acid (*d*, 1·28) at 80° gave oxalic acid (hydrated), m. p. 101°. A benzylthiuronium salt was obtained as colourless needles, m. p. 146—148°; the mixed m. p. with benzylthiuronium *cyclo*hexene-3-sulphonate (m. p. 149—150°) was 147—149°.

Hydroxy-sulphonic Acids (*Monomeric*).—The barium salts were soluble in 75% aqueous alcohol and were acetylated by heating under reflux with a mixture of acetic acid and acetic anhydride. They were saturated and did not reduce potassium permanganate, but were oxidised by nitric acid (*d*, 1·28) at 80°, giving oxalic acid. A phenylhydrazine salt, needles, m. p. 162—164°, was not the same as that produced from *cyclo*hexanol-2-sulphonic acid (either form).

Disulphonic Acids (*Monomeric*).—The barium salts were insoluble in 75% aqueous alcohol and could be obtained as a pale yellow hygroscopic uncrystallisable powder (Found: Ba, 32·8—33·6%). They were unsaturated and could be separated by fractional crystallisation of the phenylhydrazine salts from alcoholic solutions. The following fractions were obtained. (*a*) Needles, m. p. >300° [equiv. wt. of the sulphonic acids (hydrated), 128·2]; these gave a barium salt as elongated diamond-

shaped crystals, which reduced potassium permanganate in the cold. (*b*) Needles, m. p. 142—148° [equiv. wt. of the sulphonic acid (hydrated), 121], which gave an unsaturated barium salt. (*c*) Residue; an oil (equiv. wt. of the sulphonic acids, 135·5).

Sulphated Hydroxy-sulphonic Acids.—The barium salts were precipitated, by addition of alcohol to an aqueous solution, as elongated spindle-shaped crystals (Found: Ba, 32·25%). They were completely hydrolysed to the hydroxy-sulphonates by heating their aqueous solution for 4 hours at 120°.

Polymeric Sulphonic Acids.—The barium and sodium salts were yellow or brown solids which did not crystallise. The benzylthiuronium and phenylhydrazine salts were oils which did not crystallise. A more comprehensive description of the polymeric sulphonic acids produced by sulphonating the unsaturated polymer oils with dioxan–sulphur trioxide complex has been given in Part II.

Hydrolysis of the Sulphonic Acids.—Benzenesulphonic acid was completely hydrolysed to benzene by heating with 2N-hydrochloric acid at 240°, whereas the sulphonic acids derived from *cyclo*hexane and *cyclo*hexene decomposed to carbon, water, and hydrogen sulphide when subjected to this treatment.

Polymeric Oils.—These could be separated into fractions soluble and insoluble in light petroleum (b. p. 60—80°). The light petroleum-soluble polymeric oils were dark brown viscous oils containing sulphur and oxygen. They reacted with bromine by substitution, but to a lesser extent than the unsaturated polymer oils produced from *cyclo*hexene by sulphuric acid. The polymeric oils insoluble in light petroleum were dark brown asphaltic resins soluble in chloroform.

The soluble polymeric oil produced by the action of 300 g. of 18% oleum on 25 g. of *cyclo*hexene contained C 84·0, H 10·3, S 2·1, O 3·6%, had *M*, 323, absorbed 87 g. of bromine per 100 g. (with evolution of 31·3 g. of hydrogen bromide) (I.P. Method), and had bromine no. (A.S.T.M. method) 70 g. per 100 g. (226 g. per mol.).

The soluble polymeric oil produced by the action of oleum on *cyclo*hexane had bromine no. (I.P. Method) 105 g. per 100 g. (with evolution of 6·5 g. of hydrogen bromide).

Sulphur Dioxide.—The sulphur dioxide which had been absorbed in alkali was titrated with acidified iodine; the carbon dioxide was determined by liberating the acid gases, oxidising the sulphur dioxide with chromic acid, and absorbing the carbon dioxide in potassium hydroxide.

cyclo*Hexanesulphonic Acid.*—*Preparation.* *cyclo*Hexyl bromide, prepared by heating *cyclo*hexanol under reflux with 2·8 times its weight of 40% aqueous hydrogen bromide, was converted into the disulphide by reaction with sodium disulphide (Noller and Gordon, *J. Amer. Chem. Soc.*, 1933, **55**, 1090) and then oxidised by chlorine to the sulphonyl chloride (Douglass and Johnson, *ibid.*, 1938, **60**, 1486). The sulphonyl chloride was then hydrolysed by sodium hydroxide. This method gave a 42% yield of sodium *cyclo*hexanesulphonate.

It could also be prepared by treating bromo*cyclo*hexane with ammonium sulphite solution, but the yield was low (9·4%).

Reaction with oleum. 4·74 G. of barium *cyclo*hexanesulphonate were added to 50 g. of oleum containing 20% of SO_3, the temperature being maintained at 0°. A vigorous reaction ensued accompanied by evolution of sulphur dioxide. The reaction mixture was treated with barium hydroxide; the barium salts contained 0·838 g. of barium benzenesulphonate.

*Di*cyclo*hexyl.*—Prepared by hydrogenating diphenyl, this had b. p. 235—237°/767 mm., d_4^{20} 0·8885, and n_D^{20} 1·4849.

Di*cyclo*hexyl (8·37 g.) was added to oleum (100 g.) containing 20% of SO_3, and the mixture vigorously stirred for 2 hours at 0°. 3·34 G. of unchanged di*cyclo*hexyl remained; the acid layer was diluted and neutralised with barium hydroxide. The barium salts were separated into two fractions by addition of alcohol to an aqueous solution; the precipitated fraction contained approx. 2 sulpho-groups per di*cyclo*hexyl molecule, whereas the soluble fraction contained one. The salts were resinous, uncrystallisable, and partly unsaturated, and gave oily benzylthiuronium salts. No diphenylsulphonic acids could be detected.

cyclo*Hexylmethyl*cyclo*pentane.*—The mixture of isomers (1-*cyclo*hexyl-2- and -3-methyl*cyclo*pentane) obtained by polymerising *cyclo*hexene with sulphuric acid (cf. Part II) was treated with oleum. 10 G. of the mixed *cyclo*hexylmethyl*cyclo*pentanes were treated with 200 g. of oleum containing 21% SO_3 for 5 hours at 0°; 0·66 g. of unchanged hydrocarbon remained. The reaction products were similar to those obtained by the action of oleum on di*cyclo*hexyl.

Decahydronaphthalene.—The B.D.H. microanalytical reagent was shaken with sulphuric acid and then distilled, the fraction boiling between 184·5° and 187° at 765·5 mm. being collected; this had d_4^{20} 0·8706 and n_D^{20} 1·4737. The ultra-violet light absorption spectrum indicated that a small percentage (approx. 0·8%) of an alkylbenzene was present.

200 G. of oleum containing 33% of SO_3 were cooled to 0°, 26·4 g. of decahydronaphthalene were added, and the mixture was stirred vigorously. After 2½ hours, 16·35 g. of decahydronaphthalene had reacted and 14·9 g. of sulphur dioxide had been evolved. The residual decahydronaphthalene had d_4^{20} 0·8564 and n_D^{20} 1·4648. The reaction mixture was neutralised with aqueous sodium hydroxide, and the polymeric oils were extracted with chloroform and separated into fractions soluble and insoluble in light petroleum. The aqueous layer was then desalted by treatment with alcohol, and the desalted material separated into fractions soluble and insoluble in 75% aqueous acetone. The sodium salts were brown non-crystalline powders which decolorised bromine water and potassium permanganate. The salts which were soluble in 75% aqueous acetone were heated at 120° with 2N-hydrochloric acid; a small amount of oil was produced whose ultra-violet light absorption spectrum indicated that naphthalene was absent. The salts were then heated with 2N-acid at 180° and at 230°. A small yield of naphthalene was obtained in addition to a considerable quantity of carbon. The naphthalene was remarkably pure, melting at 79—80° (mixed m. p. with pure naphthalene, unchanged). This indicated the presence of naphthalene-2-sulphonic acid. Naphthalene-1-sulphonic acid would hydrolyse completely at 120° in the presence of 2N-hydrochloric acid, whereas naphthalene-2-sulphonic acid is not hydrolysed below 170°. Tetrahydronaphthalenesulphonic acids also hydrolyse at 170—180°, but they were not present in the reaction mixture. The fraction insoluble in 75% aqueous acetone also produced a little naphthalene on hydrolysis at 180—230°.

TABLE I.

Action of Oleum on cyclo*Hexene.*

cyclo-Hexene, g.	Oleum. g.	Oleum. %SO_3.	Temp.	SO_3 (g.) per 100 g. of *cyclo*-hexene.	*cyclo*-Hexyl hydrogen sulphate, %.	Polymeric oil, soluble in light petroleum, %.	Polymeric oil, insoluble in light petroleum, %.	Sulphated sulphonic acids, %.	Di- and poly-sulphonic acids, %.	Mono-sulphonic acids, % (excluding $PhSO_3H$).	Benzene-sulphonic acid, %.
60	100	20	0°	5·54	54·10	25·10	2·48	2·08	1·85	1·25	Nil
60	100	20	40	9·70	8·77	—	—	5·0	1·20	2·13	Nil
60	100	20	90	—	Nil	—	—	2·33	0·77	1·37	Nil
41	100	20	0	8·83	34·40	40·80	8·83	3·50	2·68	1·20	Nil
41	100	20	40	14·90	2·34	65·20	14·40	6·32	1·63	1·20	Trace
25	300	18	0	37·80	Nil	11·20	7·10	11·2	66·0	9·2	4·36

TABLE II.

Action of Oleum on cyclo*Hexane.*

cyclo-Hexane, g.	Oleum. g.	Oleum. %SO_3.	Temp.	SO_3 (g.) per 100 g. of *cyclo*-hexane.	Unchanged *cyclo*-hexane %.	Polymeric oil, soluble in light petroleum, %.	Polymeric oil, insoluble in light petroleum, %.	Sulphated sulphonic acids, %.	Di- and poly-sulphonic acids, %.	Mono-sulphonic acids, % (excluding $PhSO_3H$).	Benzene-sulphonic acid, %.
12·5	225	21	10°	78·75	14·8	7·59	4·35	24·5	26·43	8·0	1·60
31·7	200	61	10	73·25	28·5	3·38	2·05	1·36	36·8	9·91	1·89

The yields of all components, except SO_3, are based on equivalent amounts of *cyclo*hexene or *cyclo*hexane.

Summary of the products from decahydronaphthalene.

	%.*
Polymeric oil soluble in petroleum	5·14
Polymeric oil insoluble in petroleum	0·78
Sulphonic acids (equiv. wt. 209·3. Sodium salts soluble in 75% aqueous acetone)	44·0 [a]
Sulphonic acids (equiv. wt. 168·1. Sodium salts insoluble in 75% aqueous acetone)	22·1 [b]
Naphthalene-2-sulphonic acid	4·2
Unidentified naphthalene-sulphonic acids	1·2

* The yields are based on equivalent amounts of decahydronaphthalene.
[a] Excluding 2-$C_{10}H_7 \cdot SO_3H$. [b] Excluding naphthalenesulphonic acids.

Tetrahydronaphthalene and its monosulphonic acids (cf. Schroeter, *Annalen*, 1922, **426**, 83) were converted into an unidentified tetrahydronaphthalenedisulphonic acid, probably the 1 : 3-derivative, on treatment with excess of oleum, even at 35°. Its barium salt crystallised from water as the monohydrate which became anhydrous at 120°. It gave a phenylhydrazine derivative as hexagonal plates, m. p. 198—199° (decomp.), from alcohol. The disulphonic acid was hydrolysed to tetrahydronaphthalene by 2N-hydrogen chloride at 180°. The ultra-violet light absorption spectrum showed absence of naphthalene.

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[*Received, February 11th*, 1949.]

NOTES.

Action of a Mixture of Acetic Anhydride and Sulphuric Acid on an Acetic Acid Solution of cyclo*Hexene.*

By R. SPERLING.

THE products of this reaction, first described by Friese (*Ber.*, 1931, **64**, *B*, 2103), have now been identified as *cis-cyclo*hexanol-2-sulphonic acid and *cyclo*hexene-1-sulphonic acid. Friese, however, isolated *cis*-cyclohexanol-2-sulphonic acid only as its barium salt. If the mother-liquor are concentrated, crystals of barium *cyclo*hexene-1-sulphonate separate and can be purified by extraction with 75% aqueous alcohol, followed by recrystallisation from 50% aqueous alcohol.

This reaction is of interest as *cyclo*hexene-1-sulphonic acid cannot be obtained by the action of a mixture of acetic anhydride, sulphuric acid, and acetic acid on *cis-cyclo*hexanol-2-sulphonic acid. It is probable that acetic anhydride reacts with sulphuric acid to form a mixed anhydride (Russell and Cameron, *J. Amer. Chem. Soc.*, 1938, **60**, 1345) which then adds to *cyclo*hexene forming *cis-* and *trans-*isomers of acetoxy*cyclo*hexanol-2-sulphonic acid, which hydrolyse to give *cis-cyclo*hexanol-2-sulphonic acid and *cyclo*hexene-1-sulphonic acid, respectively. There is no experimental evidence in support of this, but, in a similar reaction between sulphuryl chloride and *cyclo*hexene in the presence of acetic anhydride and acetic acid, *cis-* and *trans-*isomers of 2-chloro*cyclo*hexyl acetate are formed (Friese and Djiany, *Ber.*, 1938, **71**, *B*, 667).

Experimental.—(M. p.s are corrected.) *cyclo*Hexene (32 g.) was added to a mixture of acetic acid (130 ml.) and concentrated sulphuric acid (25·5 ml.), cooled to −20°, and acetic anhydride (150 ml.) then added. A slight rise in temperature occurred and the mixture became reddish-brown. After being kept overnight at room temperature, the mixture was poured into 500 ml. of ice water, and the acetic acid removed under reduced pressure. The residue was neutralized with barium hydroxide, and the precipitated barium sulphate filtered off. The filtrate was evaporated to small bulk on the steam-bath, whereupon barium *cis-cyclo*hexanol-2-sulphonate (25·8 g.) crystallised; this was recrystallised from water. Barium *cyclo*hexene-1-sulphonate was obtained on concentrating the mother-liquors and was purified by extraction with 75% aqueous alcohol and subsequent recrystallisation from 50% aqueous alcohol (yield, 33·0 g.).

Barium cis-cyclo*hexanol-2-sulphonate.* The above product was identical with that produced by the action of hydrogen sulphites on *cyclo*hexene oxide (Found : Ba, 27·66. Calc. for $C_{12}H_{22}O_8S_2Ba$: Ba, 27·7%). It led to a phenylhydrazine salt, diamond-shaped plates, m. p. 140—141°, alone or mixed with an authentic specimen.

Barium cyclo*hexene-1-sulphonate.* The above product crystallised from water or aqueous alcohol as hexagonal plates (Found : Ba, 28·7. Calc. for $C_{12}H_{18}O_6Ba,H_2O$: Ba, 28·76%), which became anhydrous at 130°. The aqueous solution decolorised potassium permanganate and bromine water, barium sulphate not being precipitated by the latter reagent. Oxidation with nitric acid (*d* 1·28) at 80° gave adipic acid, m. p. 151° (equiv., 73). It led to a benzylthiuronium salt, needles, m. p. 150—151° alone or mixed with an authentic specimen, and a phenylhydrazine salt, needles, m. p. 141—143°.

*cis-cyclo*Hexanol-2-sulphonic acid was sulphated by sulphuric acid, and the barium salt of the resulting *cis*-2-sulpho*cyclo*hexyl hydrogen sulphate converted into the sodium salt by the addition of the calculated amount of sodium sulphate. The sodium salt was heated at 170° for 6 hours, the resulting acidic product dissolved in water, neutralized with sodium hydroxide, evaporated to small bulk, and treated with 3 volumes of alcohol to precipitate sodium sulphate, which was filtered off. When the filtrate was evaporated to small bulk, large rectangular crystals of sodium *cyclo*hexene-1-sulphonate monohydrate crystallised and were purified by recrystallisation from water. Yield, 3 g. The barium salt of *cis*-2-sulpho*cyclo*hexyl hydrogen sulphate gave 27·3% of sodium *cyclo*hexene-1-sulphonate (Found : sulphated ash content of anhydrous salt, 38·6. Calc. for $C_6H_9SO_3Na$: ash, 38·55%). The

aqueous solution decolorised potassium permanganate and bromine water, and oxidation with nitric acid gave adipic acid, m. p. 151°. The benzylthiuronium salt formed needles, m. p. 150—151°.

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Preparation of cis-cyclo*Hexane*-1 : 2-*disulphonic Acid.* By R. SPERLING.

THE action of ammonium hydrogen sulphite solution (pH 2·2—5·4) on *cyclo*hexene in the presence of oxygen gives *cis*-cyclohexane-1 : 2-disulphonic acid. If the pH of the mixture is too high, *cyclo*hexanesulphonic acid is produced instead. The acid was found to be identical with that produced by oxidizing 1 : 2-*cyclo*hexylene dithiocyanate with nitric acid. The low solubility of the barium salt in water, and its inability to lead to a benzylthiuronium salt derivative, are indicative of hydrogen bonding (cf. this vol., p. 1925).

Kharasch and his collaborators (*J. Amer. Chem. Soc.*, 1939, **61**, 3092) proposed a radical mechanism for the reaction of hydrogen sulphites with unsaturated compounds, in which a hydrogen sulphite free radical is produced by the removal of an electron from a hydrogen sulphite ion, the free radical then adding to the unsaturated carbon atom forming a free radical complex. In the normal course of the reaction, a hydrogen atom is acquired by the complex, thus giving a saturated sulphonic acid. The reaction between *cyclo*hexene and ammonium hydrogen sulphite solution of pH 2·2—5·4 is unusual in that the free-radical complex appears to acquire a second hydrogen sulphite free radical, forming a disulphonic acid.

Experimental.—(M. p.s are corrected.) *Action of ammonium hydrogen sulphite on* cyclo*hexene. cyclo*Hexene (12 g.) was shaken with 2N-ammonium hydrogen sulphite solution (pH adjusted to 3·9 by addition of SO_2) (200 ml.) for 17 days at room temperature, ammonium persulphate (0·1 g.) being added as catalyst and the space above the liquid filled with oxygen (replenished at intervals since it was absorbed during the reaction). The mixture was then heated to the b. p., barium hydroxide added until no more ammonia was evolved, the excess of barium hydroxide neutralised with sulphuric acid, and the precipitated barium sulphate and sulphite were filtered off. The filtrate was evaporated to small volume, and the resulting crystals recrystallised from water. 8·6 G. of *barium* of cis-cyclo*hexane*-1 : 2-*disulphonic acid dihydrate* were obtained as colourless needles (Found : Ba, 32·8. $C_6H_{10}S_2O_6Ba,2H_2O$ requires Ba, 33·05%). The solubility of the salt in water is 0·3 g. per 100 ml. at 20°. It does not lead to a benzylthiuronium salt. The phenylhydrazine salt is obtained as colourless elongated rectangular plates, m. p. 264—265°, recrystallised from 75% aqueous alcohol.

Yields of barium *cis-cyclo*hexane-1 : 2-disulphonate and *cyclo*hexanesulphonate, respectively, were : at pH 5·4, 0·65 and 4·1 ; at pH 3·9, 8·6 and 0 ; at pH 2·2, 5·5 and 0 g.

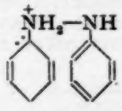
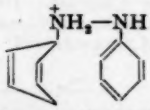
Synthesis of cis-cyclo*Hexane*-1 : 2-*disulphonic acid.*—1 : 2-*cyclo*Hexylene dithiocyanate was prepared by the action of thiocyanogen on *cyclo*hexene at 0° (Dermer and Dysinger, *J. Amer. Chem. Soc.*, 1939, **61**, 750). Recrystallisation from alcohol gave colourless crystals, m. p. 57·5° (Found : S, 33·2. Calc. for $C_8H_{10}N_2S_2$: S, 32·4%). To 2·8 g. of dithiocyanate were added 20 ml. of nitric acid (*d* 1·28) containing 0·1% of ammonium vanadate, and the mixture was heated at 80° for 1 hour. Neutralisation with barium hydroxide precipitated the crude barium disulphonate which crystallised from water as colourless needles (dihydrate) (Found : Ba, 33·37%) ; yield, 5·7 g. (97%). The barium salt becomes anhydrous on heating to 120°. The derived phenylhydrazine salt formed colourless elongated plates, m. p. 264—265° alone or mixed with that described above.

The author thanks the Board and Management of Messrs. Manchester Oil Refinery Ltd. for permission to publish this work.—CHEMICAL RESEARCH DEPARTMENT, MANCHESTER OIL REFINERY LTD. [*Received, February 11th*, 1949.]

The Benzidine Transformation. By D. LL. HAMMICK and S. F. MASON.

RECENTLY a mechanism for the benzidine transformation was proposed by us (*J.*, 1946, 638), in which an attempt was made to overcome the stereochemical difficulties inherent in any such mechanism.

We suggested that if appreciable *p*–*p*′-bonding takes place before the fission of the N–N bond, structures of the type (I) must play a large part in the activated transition hybrid, because, with an angle of 120° to the *p*-quinonoid nucleus for the C–NH_2^+ bond, it becomes possible for the *pp*′-carbon atoms to approach to within 1·50 A. of each other, *i.e.*, to well within bonding distance (C–C, 1·54 A.).

(I.)   (II.)

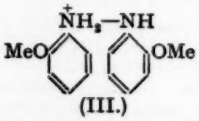
Dewar (*J.*, 1946, 777 ; also " The Electronic Theory of Organic Chemistry," O.U.P., 1949) has entirely misrepresented our views, stating that we propose a boat-shaped quinonoid structure of the type (II). Such a structure was not even mentioned, much less discussed, by us in our paper. Structures of the type (II) would of course bring the *pp*′-carbon atoms into a proximity even closer than 1·50 A., but, if appreciable resonance with benzenoid structures occurs, the quinonoid ring must be sensibly planar.

Dewar suggests that the observed range of activation energies for the benzidine transformation (11—19 kcals.) definitely rules out our mechanism, since the loss of resonance energy in the benzene ring (39 kcals.) would render the activation energy prohibitively high (we assume in this instance that he

refers to our actual mechanism, and not to his version of it). The advantage of any continuous mechanism proposed for the benzidine transformation is surely that the energy released by the formation of the *pp'*-linkage (58·6 kcals.) effectively lowers the activation energy required for the fission of the N–N bond (23·6 kcals.) and other postulated electron shifts, in this case the transition from a benzenoid to a *p*-quinonoid nucleus (32·2 kcals.). Discontinuous mechanisms, such as that proposed by Dewar (*loc. cit.*), have no such advantage. His proposed initial stage, the fission of the N–N bond, requires an energy higher than any of the observed activation energies.

Dewar (*op. cit.*, p. 236) further criticises the mechanism suggested by us on the grounds that it does not account for other rearrangements of *N*-substituted anilines. Apart from the benzidine transformation, migration to other nuclei has been reported in nearly all other cases of *N*-substituted anilines, so perhaps it is not unreasonable to postulate a special mechanism for the benzidine case.

Finally, Dewar (*loc. cit.*) finds the rates of rearrangement of substituted hydrazobenzenes to be in the order (III) $\geqslant$ (IV) > (V), and suggests that a reverse order would be expected on the Robinson mechanism, of which our mechanism is a modification.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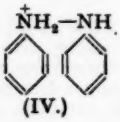
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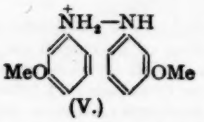
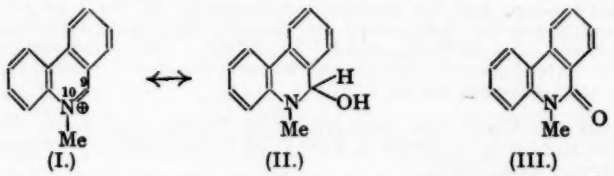

(V.)

In fact the predominating electromeric effect ($-E$) of the methoxyl group would be expected to promote the formation of a structure of type (I) in the case of (III), and to repress it in the case of (V), thus giving the observed order in the rates of rearrangement.—The Dyson Perrins Laboratory, University of Oxford, and The Museum of the History of Science, University of Oxford. [*Received, February* 21*st*, 1949.]

The Ionization of Quaternary Phenanthridine Bases. By D. Magrath and J. N. Phillips.

The ionization constants of phenanthridine and its primary amino-derivatives have recently been published (Albert, Goldacre, and Phillips, *J.*, 1948, 2240). The ionization constants of some simple phenanthridinium compounds are now reported. The results obtained may contribute to an understanding of the mode of action of the trypanocidal phenanthridines, all known examples of which are quaternary (Walls, *J. Soc. Chem. Ind.*, 1947, **66**, 182T).

The ionization measured was the pK_a^B, *i.e.*, the ionization constant expressing the equilibrium between (I) and the corresponding non-ionized carbinol (II). This ionization is of the type discussed by Goldacre and Phillips (this vol., p. 1724) for the triphenylmethanes and the quaternary acridine bases. Because carbinols of the type (II), when not substituted in the 9-position, could be biologically oxidized to non-basic ketones of the type (III), 9 : 10-*dimethylphenanthridinium chloride* was investigated as well as 10-*methylphenanthridinium chloride*. The results given below show that both these substances are completely ionized at pH 7.


(I.) (II.) (III.)

The measurements were made absorptiometrically in a series of aqueous buffers, as described by Goldacre and Phillips (*loc. cit.*) at 25° ± 1° and a concentration of $1·3 \times 10^{-5}$ M. The pK_a (equilibrium) of 10-methylphenanthridinium chloride was 10·4 ± 0·2 and that of the 9 : 10-dimethyl derivative 10·1 ± 0·2.

9 : 10-*Dimethylphenanthridinium Chloride*.—9 : 10-Dimethylphenanthridinium iodide (3 g.; Pictet and Hubert, *Ber.*, 1896, **29**, 1185) in water (180 ml.) was heated under reflux and stirred mechanically with 1·5 equivalents of freshly precipitated silver chloride for 2 hours, in subdued artificial light. After filtration, the filtrate was evaporated to give a solid, m. p. 245°, free from iodine. This was recrystallized from aqueous acetone, giving pale yellow crystals of 9 : 10-*dimethylphenanthridinium chloride*, m. p. 248° (76%) (Found : N, 5·8. $C_{15}H_{14}NCl$ requires N, 5·75%).

10-*Methylphenanthridinium Chloride*.—10-Methylphenanthridinium iodide, similarly treated, gave 10-*methylphenanthridinium chloride* (80%) as pale yellow hydrated crystals, m. p. *ca.* 215° (decomp.) (Found : N, 5·7. $C_{14}H_{12}NCl,H_2O$ requires N, 5·65%).—The University, Sydney. [*Received, February* 3*rd*, 1949.]

The Reaction of "Copper Hydride" with Acid Chlorides. By E. A. Braude.

It has been claimed (Chiozza, *Annalen*, 1853, **85**, 232; Wohl and Mylo, *Ber.*, 1912, **45**, 328) that benzaldehyde is formed in the reaction between "copper hydride" and benzoyl chloride, and that the reaction with acetyl chloride similarly gives acetaldehyde which under the conditions employed is then reduced to ethanol and converted thence into ethyl acetate. Copper hydride is an endothermic compound (cf. Sieverts and Gotta, *Annalen*, 1927, **453**, 289) and the reaction R·COCl + CuH ⟶ R·CHO + CuCl is thermodynamically feasible; it therefore appeared worth while to investigate its

possible synthetic applications, especially in view of the successful use of other metal hydrides as reducing agents for organic compounds (cf. Nystrom and Brown, *J. Amer. Chem. Soc.*, 1947, **69**, 1197; Chaikin and Brown, *ibid.*, 1949, **71**, 122).

The usual procedure for the preparation of copper hydride (cf. Vorländer and Meyer, *Annalen*, 1902, **320**, 122) consists of the reduction of copper sulphate with sodium hypophosphite in dilute sulphuric acid at *ca.* 50°, filtration of the brown precipitate, and washing with alcohol and then ether. When the air-dried product (15 g.) thus obtained was heated under reflux for 2—3 hours with a solution of freshly distilled benzoyl chloride (18 g.) in *n*-hexane or ether, hydrogen was evolved and the products obtained were some unchanged benzoyl chloride, benzoic acid (11 g., 70%), and a small proportion of ethyl benzoate (2 g., 10%), but no trace of benzaldehyde could be detected. The inorganic residue consisted largely of cuprous chloride. The same result is obtained if the reaction is carried out in an atmosphere of nitrogen or in an autoclave, in the absence of solvent. The benzoic acid is therefore *not* produced by the oxidation of benzaldehyde formed as an intermediate.

Copper hydride is known to contain water and to decompose explosively when dried over dehydrating agents (cf. Sieverts and Gotta, *loc. cit.*). The reaction with benzoyl chloride thus appears to be a simple hydrolysis to give benzoic acid, followed by interaction of the hydrogen chloride liberated with the hydride. The production of ethyl benzoate is due to the tenacious retention of some ethanol after the washing; if the moist hydride is washed with acetone, followed by ether, no ethyl benzoate is obtained. The reaction of the acetone–ether washed hydride (15 g.) with freshly distilled acetyl chloride (20 g.) in ether similarly gave only a little unchanged acetyl chloride and acetic acid (12 g., 80%). The acetone–ether washed hydride was found to contain *ca.* 60% of copper, corresponding to the composition $CuH,2H_2O$. Although it has been stated (Müller and Bradley, *J.*, 1926, 1669) that the crystal structure of copper hydride is independent of the water content, it appears that two molecules of water form an essential part of the compound but can be partly replaced by ethanol.—Imperial College of Science and Technology, London, S.W.7. [*Received, January 26th*, 1949.]

OBITUARY NOTICE.

THE REV. WILLIAM HUGHES.

1890—1948.

THE REVEREND WILLIAM HUGHES was born in 1890, the son of William Hughes, Esq., a farmer in Anglesey. He was educated at the County School, Llangefni, and was elected to a scholarship at Jesus College, Oxford, in 1910. He read for the Honours School of Natural Science (Chemistry) and was placed by the examiners in the Second Class in 1914. He stayed on in Oxford working under the supervision of the writer for the B.Sc. Degree, which he achieved with a research on The Vapour Pressures of Saturated Salt Solutions, in which he showed skill and resource.

Although he might well have continued as an active and conscientious researcher, he had strong religious feelings and these led him to read for and take Holy Orders in 1916. He served for a short time as a curate at Wrexham, but the great need for Science teachers in the 1914—1918 war led him to undertake school work where he found a field of service consonant with his high principles. He was Science Master at Bedford School from 1917 to 1925, and from 1925 until his death at King Edward's School, Southampton. Having thus returned to the laboratory he found time, in spite of his busy life of teaching, to carry out further research, and an experimental paper on the action of salt solutions on magnesium metal was published in this Journal. He also became more interested in theoretical work and published several communications on the application of the law of mass action to salt solutions and on some aspects of valency.

In his later years, Hughes became very reserved and somewhat aloof, but Mr. Arnold, the Headmaster of King Edward's School, records that he inspired gratitude, particularly among his scholarship pupils, to whom he was affectionately known as " Father William."

Much sorrow clouded his later years; his daughter Gwynneth, to whom he was devoted, was accidentally killed while on military service, and his only son was attacked by disease which necessitated his removal to the milder climate of South Africa. Shortly afterwards his wife also died, leaving him completely alone. He continued his school work until a few days before his death, for he was struck down suddenly and died soon after entering Southampton Hospital.

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